ANNUAL MEETING: CARDIFF, JULY 9—17

DOES NOT CIRCULATE

UNIVERS OF MICHIG JUN 30 19 MEDICA LIBRAR

BRITISH MEDICAL JOURNAL

JOURNAL OF THE BRITISH MEDICAL ASSOCIATION

SATURDAY JUNE 13 1953

TABLE OF CONTENTS

Parenteral Hexamethonium in Hypertension BRENDA MORRISON, M.D. 1291

Effects of Hexamethonium on Normal Individuals in Relation to Its Concentration in the Plasma BRENDA MORRISON, M.D., and W. D. M. PATON, B.M. 1299

Farmer's Lung T. C. STUDDERT, M.D., M.R.C.P. 1305

Intractable Gastric Crises Relieved by Chordotomy G. O. MAYNE, M.B., D.P.H. 1309

Toxic Effects of Phenylbutazone J. R. NASSIM, B.M., F.R.C.P., and THOMAS PILKINGTON, M.D., M.R.C.P. 1310

Toxic Effects of Phenylbutazone J. C. LEONARD, M.D. 1311

Ethopropazine Hydrochloride in Treatment of Cerebral Palsy R. G. MITCHELL, M.B., M.R.C.P.Ed., D.C.H. 1313

Adrenaline Necrosis G. LESLIE, M.D., and D. MCPHEE, M.D. 1315

MEDICAL MEMORANDUM

Torsion of a Mesenteric Lymphatic Cyst. N. V. ADDISON, M.B., Ch.B. 1316

BOOK REVIEWS 1317

REFRESHER COURSE

Intermittent Claudication. J. B. KINMONTH, M.S., F.R.C.S. 1325

GENERAL ARTICLES AND NEWS

Medical Coronation Honours 1328
BRITISH EMPIRE LEPROSY RELIEF ASSOCIATION 1327
MEDICINE UNDER THREE QUEENS 1329
CLIMBING EVEREST 1329
NOVA ET VETERA 1330
VITAL STATISTICS 1339
MEDICAL NEWS 1341
QUESTIONS AND COMMENTS 1343

OBITUARY

C. B. Levick, O.B.E., M.B., Ch.M., F.R.C.P.; E. T. Roberts, M.D., F.R.C.P.Ed., F.R.F.P.S., D.P.H.; Hilda J. Gardner, M.B., B.S.; Sir Robert G. Archibald, C.M.G., D.S.O., M.D.; Maxwell Smellie, L.R.C.P.Ed.; E. R. Desoutter; J. A. Gaynor, M.B., F.R.C.S.I.; P. G. Quinton, M.D. 1336–8

LEADING ARTICLES

Prognosis and Treatment of Hypertension 1319
Disease, Race, and Civilization 1320

ANNOTATIONS

Doctors on Everest 1321
Toxic Effects of Phenylbutazone 1322
Influenza as a World Problem 1322
Public Health Award 1323
The Painful Shoulder 1323
Dr. Brock Chisholm's Adieu to W.H.O. 1324

SUPPLEMENT

Full Contents on First Page of Supplement

Cardiff and its Environs. ROBERT D. OWEN, F.R.C.S. 273
The B.M.A. in Committee 276
The Winchester Address 277
Correspondence:
The Registrar Problem. R. M. FORRESTER, M.B., and JOHN N. WALTON, M.D. 279
The Extraordinary General Meeting. R. W. COCKSHUT, M.B. 279
The G.P. and the Industrial Medical Officer. RONALD PETERS, M.R.C.S. ..280

CORRESPONDENCE

Misuse of Drugs in Tuberculosis. W. E. SNELL, M.D. 1331
Anticoagulants in Myocardial Infarction. C. PAPP, M.D.; L. POLLER, M.B. 1331
Poliomyelitis in Copenhagen. GEOFFREY ORGANE, M.D. 1331
Acute Malaria Probably Precipitated by A.C.T.H. JOHN LOWE, M.D. 1332
Relief of Pain in Childbirth. JOHN E. ELAM, M.R.C.S. 1332
Haemophilia with Respiratory Obstruction. MICHAEL N. TEMPEST, F.R.C.S.Ed. 1332
Treatment of Ringworm of the Scalp. W. A. DEWAR, M.D. 1333
Intestinal Reflux into the Bile Passages. I. A. HARRIS, M.B. 1333
Importance of Post-mortem Examinations. G. L. DAVIES, M.R.C.S. 1334
Adrenaline Cream. LOUIS MOSS, M.R.C.S. 1334
Subcostal Pain Following Controlled Respiration. G. M. WYANT, M.D. ..1334
The Floating Spleen. J. F. RILEY, M.D. 1335
Orthopaedics and its Name. R. D. LAWRENCE, M.D. 1335

MEDICO-LEGAL

Vicarious Liability 1338

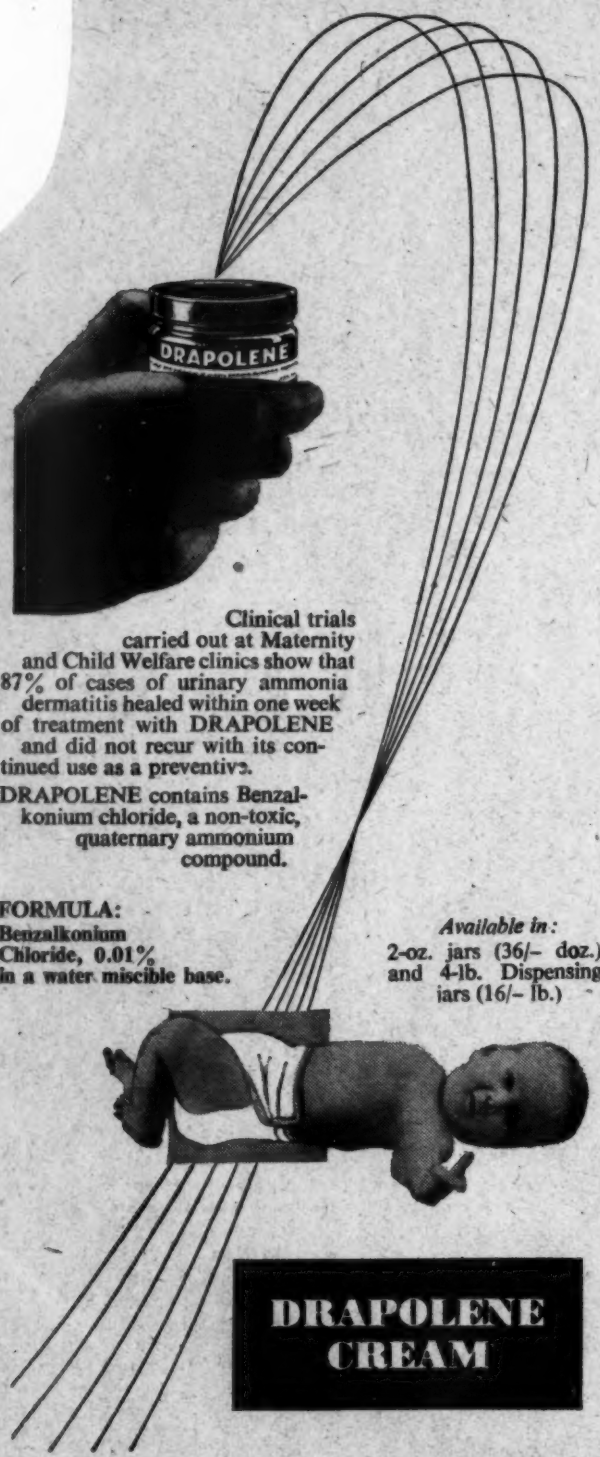
BRITISH MEDICAL ASSOCIATION, TAVISTOCK SQUARE, LONDON, W.C.1

No. 4823, WEEKLY, PRICE 3/-

Copyright

REGISTERED AS A NEWSPAPER

RINARY AMMONIA DERMATITIS



Clinical trials carried out at Maternity and Child Welfare clinics show that 87% of cases of urinary ammonia dermatitis healed within one week of treatment with DRAPOLENE and did not recur with its continued use as a preventive.

DRAPOLENE contains Benzalkonium chloride, a non-toxic, quaternary ammonium compound.

FORMULA:
Benzalkonium Chloride, 0.01% in a water miscible base.

Available in:
2-oz. jars (36/- doz.) and 4-lb. Dispensing jars (16/- lb.)

DRAPOLENE CREAM

Literature available on request from the Medical Department.

CALMIC LIMITED
CREWE HALL · CREWE · Tel. 3251-5

You can't blame anyone for liking

Youngs Potted Shrimps

Straight from the sea—caught, peeled and potted in one day. A tea-time delicacy, ideal for cocktail parties or hors d'œuvre.

YOUNG'S POTTED SHRIMPS. *The Fisheries, Cartmel, Morecambe Bay. From high-class Stores in principal towns. Write for address of nearest stockist.*

Cutting the coat to suit the cloth

With insurance policies as with clothes—it's the well-fitting ones that give the greatest satisfaction. The many ready-made policies often do not meet the needs of the individual. We have always borne this in mind when planning our policies. To keep them flexible rather than rigid; and to plan them personally to fit both the needs—and the pocket—of the prospective policyholder. If you are concerned for your future or for the future of your dependants, see how simple it is to guarantee now what you need. For example, at the age of 25 by setting aside the modest sum of £5 a month we could provide:

FOR YOU

In 20 years a cash sum of £1,000 plus profits.
Should you become disabled, your premiums cease during disability and an income of £10 monthly is paid to you.

FOR DEPENDANTS

Benefits up to a maximum of £3,400. Immediate cash payment of profits plus Pension of £10 monthly for balance of 20 years £2,400
Plus cash at end of Pension period .. £1,000
£3,400

This type of plan is bringing PEACE OF MIND to many men in your calling. Send for full particulars to-day.

Confederation Life Association
18 PARK LANE, LONDON, W.1

Incorporated by Special Act of Parliament of Canada in 1871 as a Limited Liability Company.

BRITISH MEDICAL JOURNAL

LONDON SATURDAY JUNE 13 1953

PARENTERAL HEXAMETHONIUM IN HYPERTENSION

BY

BRENDA MORRISON, M.D.

(From the Department of Medicine, Postgraduate Medical School of London, and Hammersmith Hospital)

Hexamethonium has now been used for over three years in the treatment of hypertension, and Table I summarizes briefly the results reported in 15 groups of patients, using hexamethonium (C6), pentamethonium (C5), and/or M & B 1863 (a homologue of hexamethonium); most investigators have used the oral route, entirely or for the major part of treatment, and incomplete realization of the value in treatment of this postural fall, one author even referring to it as an undesirable side-effect. The time which has elapsed since the last dose of hexamethonium was administered must also be of some importance when assessing the effect on the blood pressure, yet in many cases no reference to this time interval was made. It seems likely that variations

TABLE I.—*Summary of Results of Treatment of 15 Groups of Hypertensive Patients with Hexamethonium and Allied Drugs.*

Authors	No. of Cases	Route	Follow-up (Months)	B.P. Data		Drugs Used	General Opinion
				Position	Time from Dose		
Saville (1950)	5	Oral	3–6	Not stated	Not stated	C5	Symptomatically useful
Campbell and Robertson (1950)	8	I.M. and oral	1–4	Recumbent	,, ,,	C6	Favourable
McNally (1951)	9	Oral	Up to 3	Sitting	,, ,,	C6	Encouraging
Cusack and Cusack (1951)	9	,,	Not stated	,,	,, ,,	C6	,,
Locket *et al.* (1951)	34	I.M. 2/52 oral	1–3	Not stated	Averages (high and low)	C5 and C6	Unfavourable
Smirk and Alstad (1951)	53	S.C.	2–14	Standing, sitting and lying	Before and after dose	C5 and C6	Favourable (symptoms and signs)
Mackey and Shaw (1951)	15	Oral	1–10	—	—	C6	Moderate. Poor control
Fullerton and Milne (1951)	31	Mostly oral; few S.C.	1–5	Standing and lying	Not stated	C6	Doubtful
Persson (1951)	12	Oral	—	—	—	C6	Variable
Bechgaard *et al.* (1951)	12	—	—	—	—	C6	Not very good
Murphy (1951)	43	9 ,, parenteral, 34 oral	1½–11	Standing	"Standard"	C6	Favourable
Locket *et al.* (1952)	14	Mostly oral, few S.C.	Not stated	Not stated	Not stated	M & B 1863	Unfavourable
Campbell *et al.* (1952)	42	Mainly oral	2–18	,, ,,	,, ,,	C5, C6, and M & B 1863	Favourable
Blainey (1952)	34	Oral and S.C.	6–9	Variable	Variable	C6	Unfavourable
Freis *et al.* (1952)	32	S.C.	1–5	Supine	Averages of many	C6	Mixed

there is much difference of opinion concerning the benefit obtained. Only Smirk and Alstad (1951) have reported the treatment of a large number of patients for many months by subcutaneous injection, and they have no doubt that adequate control of the blood pressure can be maintained, with relief of symptoms. The present paper presents a study of a rather different group of patients treated by subcutaneous injection.

It was felt that if the value of a new remedy is in doubt, and especially when dealing with a complex condition like hypertension, the most decisive indications of its effects would be seen in severe or even hopeless cases. For this reason, and also because the treatment was felt to be too rigorous to warrant its employment in milder cases, the patients in this series were selected from the more limited numbers affected by complicated-essential, malignant, and renal hypertension.

Although it was made clear in the earliest reports on the action of the drug that there is a notable accentuation of the fall of blood pressure in the upright posture, some authors have not stated in which position their pressure readings were obtained, and there seems to have been in route of administration and recording of data might account for much of the divergence of opinion among different authors.

Conclusions reached in a study of the effects of hexamethonium bromide on normal individuals (Morrison and Paton, 1953) have been helpful in interpretation of the results reported here, and especially in the approach to the problem of tolerance to the drug.

Case Material

Of the 39 patients studied, 17 were men and 22 were women, and their ages ranged from 22 to 64 years. The patients were classified in the following manner:

Group A. Essential Hypertension Without Complications.—All this group were considered unsuitable for treatment.

Group B. Essential Hypertension complicated by (1) headaches of typical hypertensive character; (2) clinical, radiological, or electrocardiographic evidence of left ventricular enlargement; (3) central nervous system episodes, including giddy attacks, black-outs, encephalopathy, or minor cerebral vascular accidents. All group B cases were regarded as requiring treatment unless they were too old.

Group C. Pre-malignant Essential Hypertension.—Fairly rapid progression or worsening of the symptoms and signs of group B, particularly if associated with active Grade III retinopathy, qualified a patient for inclusion in this category, and made treatment an urgent consideration.

Group D. Malignant Essential Hypertension.—Arising as an acute illness in a patient who had apparently been previously healthy or developing in a known hypertensive, and with Grade IV retinopathy as an essential part of the clinical picture. All patients in this category were treated urgently and intensively.

Group E. Malignant Phase of Primary Renal Hypertension.—Clinically indistinguishable from Group D, but having a history or signs of preceding renal disease.

Group F. Chronic Hypertension Complicating Primary Renal Disease.—Includes all cases of established hypertension thought to be due to primary renal disease (glomerulonephritis or pyelonephritis) or to have followed a pregnancy toxaemia.

An open mind was preserved in treating cases in Groups E and F at first, but after some gratifying results this type was regarded as very suitable for treatment.

In classification and assessment of progress detailed fundus examinations (Keith, Wagener, and Barker, 1939) were regarded as of primary importance.

The two factors which took priority in selection were severity of the disease and youth of the patient; cases with minor complications were considered only if they were very young, and patients over the age of 55 were not treated unless the complications were such as to make the outlook very poor. At first one or two patients over the age of 60 were included, but it became evident that they were unsuitable because (1) arteriosclerosis and the related liability to thrombosis is common, (2) they stand the side-effects of the drug very badly, and (3) a drastic treatment of this kind is usually not necessary in the slowly progressive hypertension in the elderly.

An important point in selection was the mentality of the patient, as a moderate degree of intelligence and a fair capacity to co-operate were essential for long-term success.

Table II shows the incidence of fundus changes, and the range of blood pressure before treatment in the various clinical groups.

TABLE II.—*Case Distribution, Incidence of Fundus Changes, and Range of Blood Pressure Before Treatment in the Various Clinical Groups. (The Blood-pressure Figures Given are Averages for the Group of the Highest and Lowest Readings.)*

	Essential				Renal	
				Malignant		
Group:	A	B	C	D	E	F
No. of cases	0	22	1	3	4	9
Fundus changes:						
Grade I		9	0	0	0	3
,, II		8	0	0	0	2
,, III		3	1	0	0	4
,, IV		0	0	3	4	0
Average systolic blood pressures:						
Highest		240	230	240	236	253
Lowest		200	210	190	200	195
Average diastolic blood pressures:						
Highest		143	145	133	149	142
Lowest		116	135	112	125	116

Method of Treatment

Treatment was begun in hospital. The patients spent about one week under observation, during which time they were encouraged to be up and about the ward. Blood-pressure readings were obtained under conditions varying from out-patient attendance to rest in bed, and complete routine investigations were made.

Subcutaneous injection was the basis of all long-term therapy. At the start of the investigation three patients received only oral therapy for short periods; they are included in the series because they illustrate some useful points.

The response to the initial test dose gave information mainly about the sensitivity of the patient's blood pressure to a standard dose of hexamethonium. This sensitivity was a useful guide to the size of increments of dosage during stabilization, and to the level of blood pressure at which the individual patient would develop hypotensive symptoms, such as faintness.

Stabilization

In general three injections at eight-hourly intervals were given whilst the patient was in hospital, and the times of these were arranged so that the response to a dose could be followed once or twice daily. It was found that the effect of the drug could conveniently be assessed by taking the pressure just before a dose and one hour afterwards, as this is the average time for maximum effect. About once weekly the blood pressure was followed for a period of four to six hours after a dose, and the type of curve shown in Fig. 1, *a* was the general result. Half-way between the highest and lowest readings obtained is probably a fair indication of the average pressure on that particular day.

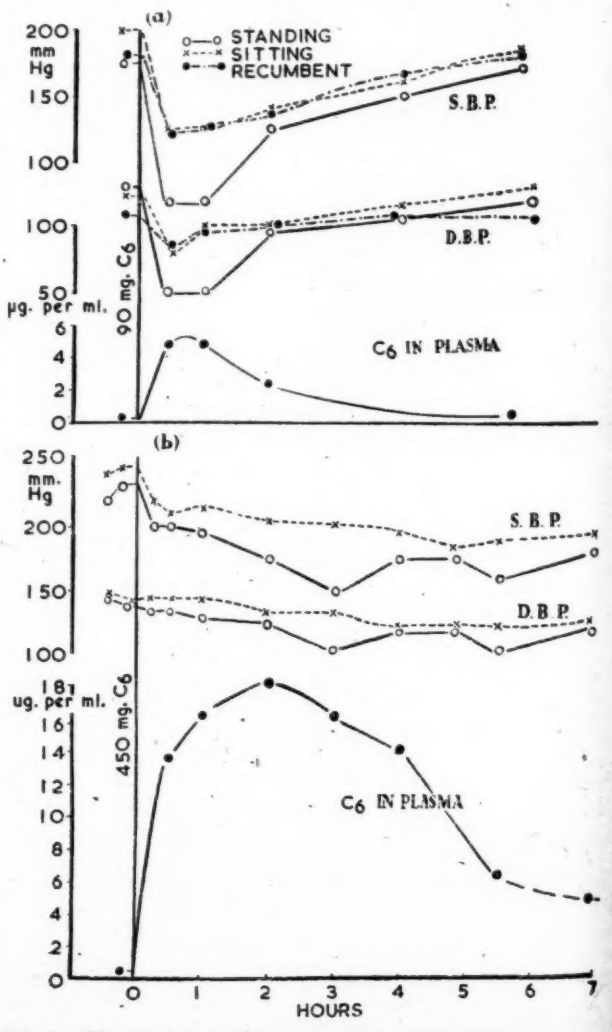


FIG. 1.—Blood-pressure curves and plasma hexamethonium concentrations (*a*) in a patient in the early stage of treatment, and (*b*) in a patient after eight months' treatment who had developed a high degree of tolerance.

The blood pressure is said to fall during sleep, and it has been argued, therefore, that a night dose of hexamethonium is not necessary; although all-night studies of the blood pressure were not made in these patients it was usually high in the morning, and when the night dose was omitted there was a tendency to hypertensive morning headache. On these grounds the treatment has been spread out over the 24 hours.

The starting dose was usually 25 to 50 mg. eight-hourly, and this was increased as necessary by increments of 25 to 50 mg. to keep the standing systolic blood pressure one hour after a dose as low as possible without the production of undue faintness; it was often possible to reduce the level to 100/60–110/70 at this point, although some patients, after having a high blood pressure for a long time, felt faint and weak with a level still above normal—for example, 140/90.

At the end of three or four weeks' treatment the development of resistance to the drug had usually slowed down, and tolerance thereafter increased only slowly and to a minor degree (see later section). The patient was then regarded as reasonably balanced and could be treated as an out-patient.

During stabilization the patients were learning to give their own injections, to measure the drug and to care for syringes; they were not discharged from hospital until they were quite confident in these procedures. If it was evident that there would be serious difficulties in the way of continuing injections at home, the patient was regarded as an unsuitable subject for therapy unless very seriously ill.

Out-patient Supervision

After discharge the patients were seen at first at weekly intervals, but when they were really confident and stabilized attendance at monthly intervals was sufficient. About half the patients were able to continue the three injections as out-patients, but some could manage a working life only with 12-hourly injections, and for them the dosage scheme was altered when they returned to work.

Criteria of Dosage

In general the lowest blood-pressure level that the patient could tolerate without being unduly incapacitated was aimed at, and the dose was adjusted with this in view. It was thought necessary to be very strict about obtaining this reduction in the pre-malignant or malignant groups, even at the cost of curtailing the patient's activities; but in group B the leading of as normal a life as possible was thought very important and the fall of the blood pressure to something like 150/100 was accepted as satisfactory. The patient's morale and the ultimate success of long-term treatment depend upon the advantages outweighing the disadvantages, and on his ability to lead a useful life; thus a too stringent regime may defeat its own ends by causing the patient to give up treatment.

General Management

To be effective hexamethonium treatment is long-term and possibly indefinite in duration, and success depends upon the attitude of the patient as much as upon effective technique. It seems essential that the patient should have (1) hypertensive symptoms or signs severe enough to make the unpleasantness and tedium of the treatment worth while; (2) a full understanding from the start that the duration of the treatment is indefinite and that it involves self-administered injections; and (3) a real desire to co-operate: without these no patient in the series continued beyond a few weeks. On the doctor's part a reasonably consistent policy is important in order to give the patient confidence, and he must be prepared and able to allot the necessary time to follow-up supervision as well as to the stabilization period in hospital.

Close contact with these patients has produced much evidence that emotional factors play an important part in determining the level of blood pressure even in organically established cases, and it was considered important that they should be given adequate opportunity to discuss their various fears, domestic difficulties, etc., in the out-patient sessions as well as in the ward.

Many of the patients had a high degree of drive and appeared to be working harder than was necessary in their circumstances. When this necessity to drive themselves was pointed out, most of them were able and willing to adjust their own affairs so as to take life more easily.

It was also evident that many of them were unusually nervous and readily agitated, but their anxiety was often projected elsewhere—for example, the patient who became aggressive and upset about faults in hospital administration turned out to be completely suppressing the fact that his mother had recently died from a hypertensive stroke, and the exacerbation of his own symptoms had dated from this event. If such situations can be elucidated and their importance indicated tactfully to the patients, the real cause of anxiety becomes clearer to them and there is a corresponding diminution of tension, emotional and vascular.

It is of course important to realize that such opportunities for dependence on and discussion with the doctor may play quite an important part in the relief of emotional tension, and thus contribute to the success of the therapy.

It was found useful in the management to give to patients on discharge a sheet of written instructions about what to do in certain eventualities and emergencies.

Results

Of the 39 patients observed, five died during treatment, and in four it was deliberately discontinued on various grounds, leaving 30 possible cases for continuing regular treatment. Of these 30, 24 have continued for periods of between three and fifteen months, and six gave up of their own accord after less than three months, but two of these have since reapplied for treatment.

Deaths During Treatment (5)

A man aged 54 (group B) developed a coronary thrombosis while on treatment; the drug was discontinued, but two weeks later he had a further coronary thrombosis, from which he died.

A man aged 57 had malignant essential hypertension with severe encephalopathy, congestive cardiac failure, and visual impairment. Treatment was begun very late in the disease, but produced considerable symptomatic improvement. After about 10 days he developed a fatal cerebral haemorrhage at a time when his next injection was due and his blood pressure therefore was probably high.

A man aged 38 had advanced malignant hypertension with congestive cardiac failure, blood urea 227 mg. per 100 ml., and diminished visual acuity. Treatment gave symptomatic relief of headache, fundus changes and vision improved, but he died of uraemia after seven weeks.

A woman aged 47 had malignant hypertension with congestive cardiac failure, severe headache, diminished visual acuity, and blood urea 86 mg. per 100 ml. She was partially relieved of all symptoms by treatment and was well enough to go home, but the congestive failure returned after three months and she died while still on treatment. The blood urea remained at 89 mg.

A man aged 22 had terminal chronic pyelonephritis and was treated only for symptomatic relief of headache; he died in a few weeks of rapidly progressive uraemia.

Four of these patients were critically ill and would have died in any case, possibly sooner without treatment, and they all obtained some symptomatic relief. The remaining case is the only example of a coronary thrombosis developing during treatment.

Treatment Discontinued Deliberately (4)

A man aged 30 (group F) had already suffered from encephalopathy and a thrombosis of the central artery of the retina, and had very severe headaches. He was one of the first patients to be treated, and received the drug only by mouth for a few weeks. The blood pressure was resistant and he required 3 g. daily to produce a moderate fall. After some trouble with constipation produced by the drug, he collapsed in the lavatory with hypo-

tension and coma. He remained unconscious for some days after the blood pressure had risen, and was left with evidence of permanent cerebral damage, particularly dysarthria.

This case drew attention to the hazards of oral therapy, and all patients have since been treated by subcutaneous injection.

In the remaining three patients subsequent experience indicated that they were really unsuitable for this form of treatment, and it was accordingly discontinued.

A man aged 61, an arteriosclerotic, was unable to co-operate; hypertension was not very severe. Treatment was persisted in for only two to three weeks.

A woman aged 57 had chronic renal hypertension, but was very labile and not progressive. She was rather unintelligent and lived too far from the hospital for adequate supervision.

A woman aged 63 had chronic nephritis with severe headaches. She had periods of mental confusion, which made her unable to co-operate in treatment outside hospital.

Patients Giving up Treatment (6)

In two of these the side-effects were very severe (excessive faintness and weakness with marked constipation, visual upset, and difficulty in micturition), and both felt worse on treatment. (One also had Sturge–Weber syndrome with epilepsy and very severe headaches, which did not improve when his blood pressure was lowered.)

Two further patients had well-marked cardiac enlargement and signs of congestive failure before treatment; they improved considerably, but gave up treatment against advice after two months. They returned with severe heart failure after three months and six weeks, and restarted treatment. They both responded again, one very remarkably (see below).

The remaining two patients who gave up were young subjects with little disability, and, having obtained symptomatic relief, decided that they did not wish to continue injections.

Patients Continuing Regular Treatment

Of these 24 patients 18 are leading active and practically normal lives, doing a full day's work and able to undertake such activities as gardening and dancing. The other six are much improved, but are still restricted in their activities. Three of these are cases of malignant hypertension, the first one having a severe degree of cardiac damage which necessitates a very quiet life, the second having a good deal of faintness and weakness but able to do some work and steadily improving, and the third being still in the initial stages of treatment, but able to get about normally. Two have other disabilities (chronic bronchitis and emphysema and aortic thrombosis causing claudication), and it is these disabilities rather than the hypertension which restrict their activity. The sixth is a 59-year-old woman who has not felt well enough to resume work in a laundry.

Details of Results

Blood Pressure

In a previous investigation of the effects of hexamethonium on normal subjects a very wide variation in sensitivity was demonstrated (Morrison and Paton, 1953). These hypertensive patients showed a similar wide scatter, but, judged on percentage fall of blood pressure, they seem to be somewhat more sensitive to an initial dose than normal individuals. The general course of the blood-pressure response (Fig. 1) was the same as in the normal individuals, with the same correspondence between the falls in the standing, sitting, and recumbent postures; the degree of postural accentuation, however, showed a considerable variation.

In the early phases of treatment, when small doses are being used, the pressure falls fairly steeply and rises again to the previous level within three to four hours. With larger doses, and usually when tolerance has developed, the maximum fall tends to occur later and to be maintained for a longer period—that is, the whole curve becomes more rounded and obtuse (Fig. 1, *a* and *b*). The similar differences in shape between the curves of plasma levels suggest that this alteration may be due largely to differences in rate of absorption with large doses.

Fig. 2 shows a typical example (Case 14) of the behaviour of the blood pressure during 14 months of treatment; data were not available for the early stages, but it will be seen

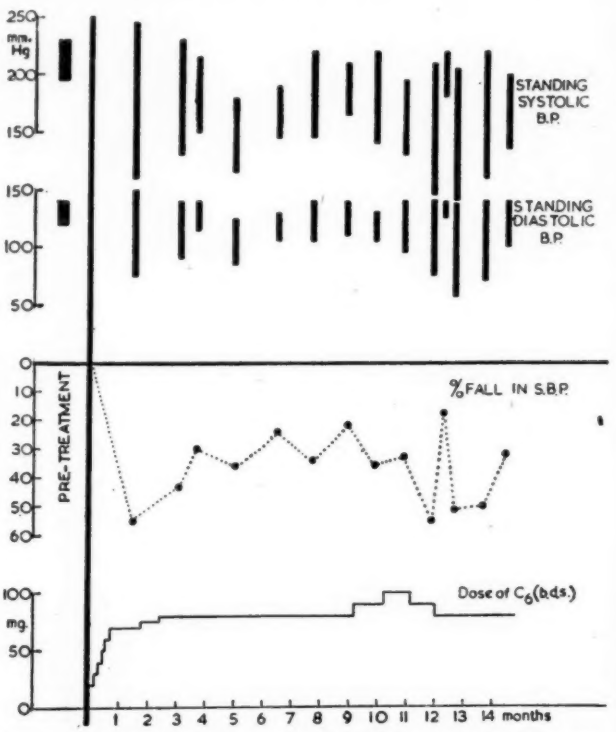


FIG. 2.—Blood-pressure response during fourteen months' treatment with hexamethonium (Case 14). The upright heavy lines show the range of pressure on the day of observation—that is, the reading taken immediately before a dose and that taken one hour afterwards; the mean for the day is taken as half-way between these two. The dotted line shows the percentage fall in the standing systolic pressure in each instance.

that after the first six weeks the response to the drug remained fairly uniform with some phasic variation from time to time. Similar behaviour was shown in all cases treated over any length of time. In Table III the blood-pressure averages before treatment are compared with the mean pressures at time of writing for 19 patients who had had regular treatment for more than three months.

TABLE III.—*Falls in Mean Systolic and Mean Diastolic Blood Pressures in 19 Patients Treated for More than Three Months (the Readings in the Standing and Sitting Postures are Averaged.)*

Case No.	Months on Treatment	Mean Systolic B.P. (mm. Hg)			Mean Diastolic B.P. (mm. Hg)		
		Before Treatment	Present	Fall	Before Treatment	Present	Fall
7	15	185	135	50	110	90	20
8	16	220	195	25	145	130	15
9	10	175	155	20	130	110	20
11	14	220	175	45	140	125	15
12	14	220	155	65	140	110	30
13	12	220	145	75	113	105	8
14	13	215	155	60	133	105	28
16	14	255	160	85	132	110	22
17	13	250	160	90	150	110	40
18	13	215	165	50	135	95	40
20	11	222	165	57	137	117	20
22	10	202	160	42	130	115	15
24	10	227	185	42	120	110	10
25	7	200	175	25	120	112	8
26	8	225	165	60	130	110	20
28	6	217	160	57	140	120	20
30	6	215	170	45	135	120	15
35	3½	210	150	60	140	105	35
36	3	210	170	40	117	100	17

Reduction in mean systolic pressure ranged from 20 to 90 mm. Hg and in diastolic pressure from 8 to 40 mm. Hg. On the out-patient days the morning dose is often two to three hours late, so that the pre-injection reading is probably higher than usual. In addition, for at least one or two hours the pressure is much lower than the mean value, as can be seen from the diagrams, and this complete or almost complete relief of hypertension, for a short period twice or thrice during the 24 hours, may have a more important effect on the course of the disease than we can assess at present.

It has been our experience that most of the tolerance (see below) which develops does so during the first four to six weeks of treatment. There remain three types of variation in the response of the patient to a constant dose :

(1) Sudden exacerbations of hypertension with litttle or no response to the usual dose have often occurred. These were very temporary, and when the patient was seen again in a day or so the response had returned to its previous level.

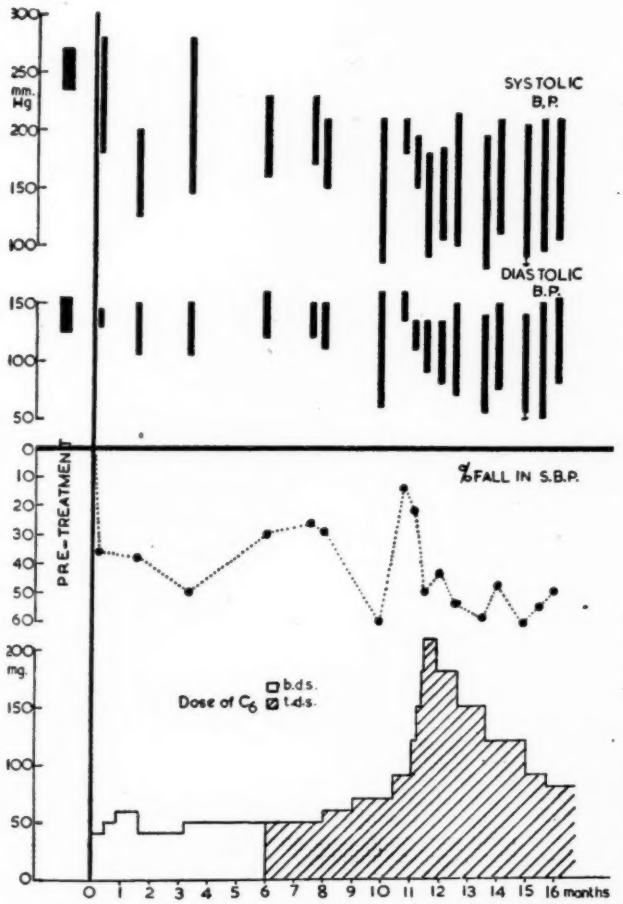


FIG. 3.—Blood-pressure response during 16 months of treatment (Case 16). The exacerbation of symptoms with diminished response to the drug began after 10½ months and lasted for some weeks (see text).

(2) Occasionally more prolonged exacerbations with diminution of response have been encountered. The best example is shown in Fig. 3, and the case history is as follows :

Case 16.—A married woman, with severe hypertension following pre-eclampsia. The exacerbation which occurred after a period of domestic stress was accompanied by a return of severe and incapacitating headaches for one week, followed in a few days by development of homonymous hemianopia, which was probably due to a cortical thrombosis. It was necessary to increase the dose threefold in order to obtain a satisfactory lowering of pressure. However, after several weeks the condition showed a steady improvement, and it was necessary, because of excessive hypotension, to reduce the dose again in stages to an amount just above that on which she had previously been stabilized for months.

(3) In addition there is a very definite increase in blood-pressure fall when other causes of peripheral vasodilatation are operating : hot weather, unwonted exercise, and especially a feverish illness have all been repeatedly observed to be associated with an extra and sometimes excessive fall in blood pressure. The splanchnic vasodilatation which follows a meal can have the same effect, and there have been many instances of a postprandial dip in the blood-pressure curve during a six-hour follow-up. On the other hand, in cold weather nearly all the patients have shown a lesser fall. Temporary adjustments in dosage have been necessary in these eventualities.

In the presence of fever about half the dose produced the usual effect. Diarrhoea and vomiting are other potent hypotensive agents, and some very great falls of blood pressure have been seen when their effect became added to that of hexamethonium ; it was deemed advisable to omit the drug altogether until the initial acute phase of the disturbance had been overcome, and then to give only about one-third of the usual dose until the blood pressure regained its former height. In both febrile and gastro-intestinal upsets the lessened requirements of hexamethonium have extended beyond the duration of the acute illness by several days, a fact which may be at least partially explained by temporary sodium depletion.

Headaches

Of the 24 patients who received regular treatment, 19 complained of typical hypertensive headaches, which in 10 were very severe and often incapacitating. They were almost completely relieved in 15, and in the other 4 they were much lessened in frequency and severity. The patients were all quite satisfied that this symptom had been greatly ameliorated by treatment. There have been quite frequent examples of development of a headache when an injection has been delayed for test purposes and in such cases the headache lessened and disappeared in parallel with the fall in blood pressure. The only example of complete failure to relieve headache was in a patient with cerebral angiomatosis.

Central Nervous System (Apart from Headache)

Recurrent giddiness was a feature in 10 of the 24 cases, and in all it seems to have disappeared. Nine had suffered from encephalopathy before treatment, and it has shown no recurrence in eight and only a very minor recurrence in the ninth, over periods of three to sixteen months. One patient had a cerebral vascular accident with almost complete recovery before treatment, and suffered a recurrence of almost identical nature whilst on treatment, but this also largely cleared up ; treatment was continued because of the generally poor outlook without it (he also has cardiac involvement), and there has been no further trouble for six months. Another patient, already mentioned, had a small occipital cortical vascular lesion during an exacerbation, but it was related to excessively high blood pressure and would possibly have been more serious in the absence of treatment.

Optic Fundus Changes

In every case of malignant hypertension, even in those dying while on treatment, the papilloedema diminished in a week or so ; later the haemorrhages absorbed and the exudates showed progressive hardening, shrinking, and clearing over three to six months.

Case 28, who had the most severe retinopathy ever seen in this department, showed a remarkable improvement after six months' treatment (Fig. 4).

Cardiac Strain

Shortness of breath on exertion was present in 13 treated patients and in 12 it was accompanied by radiological evidence of cardiac enlargement or by the electrocardio-

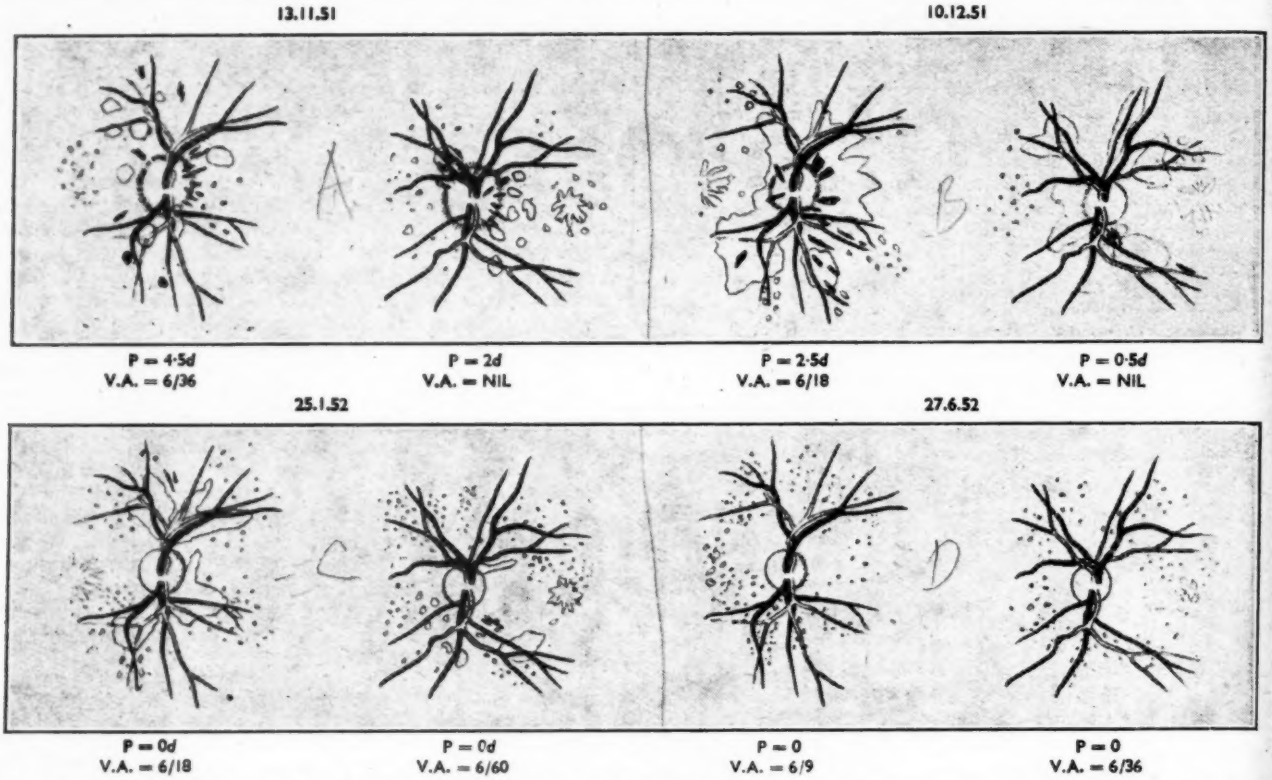


FIG. 4.—Case 28. Diagram of fundus changes in a case of malignant hypertension (*a*) before treatment, (*b*) after four weeks' treatment (temporary worsening after initial improvement), (*c*) after 10 weeks, and (*d*) after seven and a half months. P = papilloedema. V.A. = visual acuity.

graphic changes of hypertension. In the early months of treatment most of these patients reported much improvement, but two have developed a different type of dyspnoea related to changes in the lungs (see below), which is possibly a complication of long-term therapy.

Paroxysmal nocturnal dyspnoea had occurred in six patients, and three of them had frank congestive cardiac failure on admission; one of these died after three months (see above), three have had no recurrence, and the other two were freed of attacks but relapsed after discontinuing treatment; their cardiac failure again cleared up with combined hexamethonium and digitalis therapy.

In one case cardiac asthma was dramatically relieved by hexamethonium treatment alone—and relapsed as dramatically when the drug was temporarily discontinued. There was a direct correlation between the lowering of the blood pressure and the relief of dyspnoea.

In eight patients the cardiac volume was estimated before and after three to six months' treatment (method of Carl Eric Friedman, 1951). Two were within normal limits and remained so; the remainder were initially between 100 and 250 ml. per m.^{2} body surface above normal, and four of these showed a significant reduction in size—that is, more than 100 ml. per m.^{2} after treatment.

Electrocardiographic changes were followed in 22 cases. Six were normal and showed no change after 4 to 15 months; six initially showed well-marked evidence of left ventricular hypertrophy with much improvement after 3 to 16 months (Fig. 5); seven showed initially great or moderate evidence of left ventricular hypertrophy and were unchanged after 1 to 12 months; and three showed moderate degrees of left ventricular hypertrophy, which was slightly greater after 3 to 15 months' treatment.

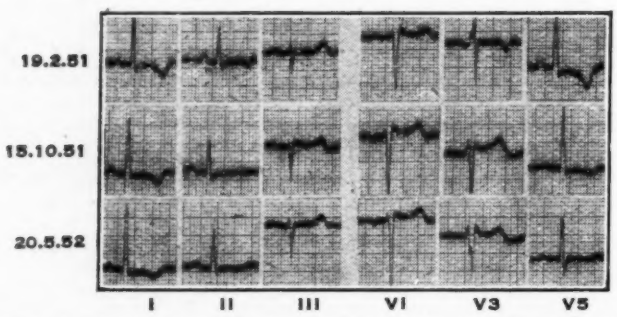


FIG. 5.—Improvement in electrocardiographic changes after 15 months' treatment with hexamethonium.

Renal Disease

Among the seven cases which had a normal blood urea before treatment there is no instance of a rise having occurred during the period of follow-up. Of the five cases which showed a raised blood urea before treatment, three have had no further rise, and in the two which have shown a slow rise over many months there has been no evidence that hexamethonium has accelerated the progress of renal disease. (Owing to slower excretion in the presence of renal impairment, injections in these cases were given only 12-hourly or even once daily.)

Treatment of Side-effects

If the disability becomes acute from any of these effects it can be relieved promptly and completely by omission of 12 to 24 hours' treatment (an advantage of first importance when comparing parenteral and oral routes of administration). Dryness of the mouth, dysphagia, difficulty of micturition, and to some extent the pupil changes are usually relieved by giving 25 to 50 mg. of the urethane of β-methylcholine ("mecothane") sublingually at the time of the injection. This drug does not seem to have much effect on the constipation, and purgatives of the phenolphthalein type or even regular omission of a dose twice weekly have been necessary in a number of patients. Bladder difficulties are relatively uncommon and are always lessened by emptying the bladder just before an injection.

Tolerance

This interesting phenomenon shows a remarkable difference in severity among different patients. All those who could be followed closely during the initial phases of treatment showed a definite diminution in response after the first test dose, but, in some, little further tolerance developed, and they were stabilized within a week or ten days and their blood pressure remained controlled at the same level of dosage for many months. At the other extreme were patients who developed rapid tolerance to the drug, which continued to increase for several weeks, but usually reached a maximum within about six to eight weeks of starting treatment and thereafter remained static; in a few patients a slow steady increase in tolerance was seen over many months. In several patients 300–450 mg. thrice daily was required to overcome the tolerance, and in one instance up to 600 mg. thrice daily has been used.

Fig. 6 shows the development of tolerance in a typical case. Each time the dose was raised a more satisfactory blood-pressure fall was obtained, but the effect fell away during the next two to three days. Between * and * in the figure two further increments of dosage had no beneficial effect for some reason which is not understood, but after three days there was a sudden return of sensitivity, and the behaviour of the blood pressure thereafter again followed the pattern indicated. Towards the end of the third week the development of tolerance slowed down, and from the fifth week onwards the patient maintained a fairly uniform response to the same dose which has now been continued for five months.

All gradations between the two extremes have been seen among different individuals. The development of tolerance in this series showed no relation to the type of disease, to initial severity of the disease, or to initial sensitivity of the patient to a test dose.

In Fig. 1, *b* the plasma levels after a dose of 450 mg. can be compared with the effects on the blood pressure in a patient with a high degree of tolerance. The expected amount of hexamethonium excreted by the kidneys over the period can be calculated from the plasma levels and from the glomerular filtration rate. In this instance the patient would be expected to excrete about 430 mg. in the eight hours of the observation. This indicates that in the presence of full tolerance there is apparently no destruction of the drug in the body, although it is obvious that the degree of lowering of the blood pressure is greatly diminished in proportion to the high plasma levels, when this is compared with the effects on normals or in a patient just beginning treatment (Fig. 1, *a*).

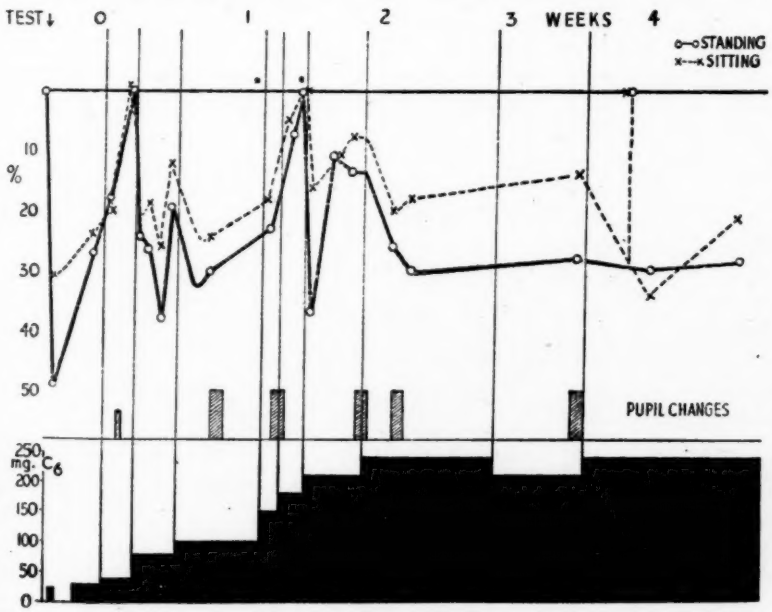


FIG. 6.—Development of tolerance to hexamethonium. Blood-pressure responses to increasing doses of the drug are shown. The heavy line indicates percentage fall in standing systolic pressure and the dotted line percentage fall in sitting systolic pressure. (Pupil changes are assessed on a points system: one point for partial and two points for complete interference with light reaction, for each hour of a four-hours observation period.)

Relationship of Tolerance to Pupil Changes

It was noticed during observation of a patient who was developing tolerance of the blood pressure to smaller doses of hexamethonium that no pupil changes were evident with a dose below 50 mg. When, however, the dose was increased to 75 mg. partial interference with pupillary function was seen, and this increased as the dose was raised, in spite of the fact that the effect on the blood pressure was lessening. The observation was extended to other patients, and in several cases in which the necessarily detailed data could be obtained it was shown that during the first few weeks pupil changes increased in proportion to the dose given and, having reached a maximum, remained maximal indefinitely. In contrast to this the blood-pressure response was showing the pattern already described (Fig. 6). The relationship between blood-pressure response, pupil changes, and dose is also shown in Fig. 6.

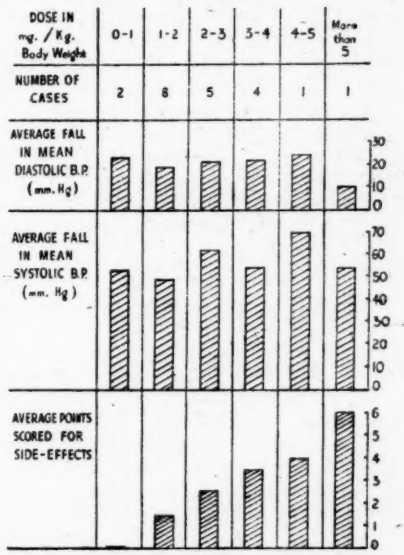


FIG. 7.—Relationship of (*a*) blood-pressure fall and (*b*) side-effects to the stabilization dose of hexamethonium. Points were given as follows for side-effects—one for moderate degrees and two for severe degrees of mouth dryness, constipation, and interference with pupillary function—maximum six points; the averages for the dose group were then calculated.

Although not lending themselves to the same easy observation as the pupils, the dryness of the mouth and the constipation, as judged by patients' complaints, showed very much the same increase in proportion to the dose of the drug as did the pupil changes.

When the 21 cases which have continued with regular treatment for more than three months are divided into groups according to their present (stabilization) dose, the average disability from side-effects (calculated from a points system) can be compared with the average fall in mean systolic and diastolic blood pressure. In short, the tolerance shown by the blood pressure does not apply to these parasympathetic effects of hexamethonium (Fig. 7).

In patients exhibiting tolerance, discontinuance of the drug for several weeks or even days was followed by an increased sensitivity, so that caution had to be used in restarting treatment if hypotensive collapse was to be avoided. However, the tolerance, which formerly took several weeks to reach a maximum, became re-established in several days and the patient again required the same high dose.

Pulmonary Complications

Since the completion of this study three patients have developed lung changes which may be a complication of long-term hexamethonium therapy. Initially all three had

malignant or pre-malignant hypertension, two had congestive heart failure, and the third was a chronic nephritic with raised blood urea (80 to 120 mg. per 100 ml.). Up to the time of development of the pulmonary changes they had been improving satisfactorily, radiological signs of cardiac failure had completely cleared, and they had returned to an active life. Dyspnoea then developed quite suddenly after fifteen, nine, and seven months' treatment; shortness of breath was pronounced on any exertion, but, in contrast to previous cardiac dyspnoea, it was relieved by lying flat.

X-ray examination showed bilateral symmetrical opacities in the lungs, in the upper zones and mid-zones. Multiple sputum examinations were negative. Because of these changes hexamethonium treatment was discontinued in these three patients, and a week later one of them died from a cerebral haemorrhage. Necropsy showed a central induration of both lungs due to extensive cornification, regarded as the result of organization of an intra-alveolar fibrinous exudate (preliminary report from Dr. Doniach). *X*-ray examination of the remaining patients in the series has not revealed any other examples of these changes.

Discussion

These cases were studied in more detail than is necessary for routine treatment; but it is evident that there are few short cuts if adequate control is to be maintained. Each patient must be stabilized individually, and there is no set formula for dosage or period of stay in hospital; the out-patient follow-up is time-consuming and really requires a special clinic. The necessary work can be tedious for both patient and doctor at times, but this has to be set against the fact that this form of therapy, when adequately carried out, is a real advance in the treatment of both malignant and complicated hypertension.

Little can be said yet about long-term results, but the recovery of four out of seven patients with malignant hypertension from acute and serious illness, and their return to a reasonably active life for periods of three, seven, nine, and fifteen months, compares favourably with previous experiences of such cases.

The complications encountered during this study have been of two kinds: the occurrence of cerebral vascular accidents in four patients who were liable to them in any case (and two of whom had had attacks prior to treatment), and the recent finding of dyspnoea and radiological lung changes in three cases.

In two out of four instances of cerebral vascular accident the blood pressure was known to be poorly controlled at the time and was almost certainly high when the incidents occurred; two of them made a functionally complete recovery.

The pathogenesis of the pulmonary changes referred to above is still obscure, and further work is in progress. There is no definite evidence that the changes are due directly to hexamethonium. Although these three patients required large doses of the drug, others who required as much or more have remained well. Regular chest *x*-ray examination and immediate attention to any complaint of increasing dyspnoea are certainly indicated in view of these developments, but, as stated, radiography of the remaining patients in the series has failed to show any instance of unsuspected lung disease.

Our feeling is that the risk of these complications should not be regarded as a contraindication to the use of hexamethonium in severely ill hypertensive patients, whose outlook in many cases is very poor. They can often be relieved of most of their symptoms and returned to a more active life.

In the less advanced but complicated cases it is quite clear that symptomatically there has been great amelioration, and most of the patients were able to lead practically normal lives, whereas they had often been incapacitated and wretched because of recurrent headaches for long periods. To attribute the continued relief that has beeen attained in these cases merely to the placebo effect of injections must seem nonsensical to anyone who has had experience of trying to alleviate these headaches by multitherapy in the past. The fact that the headaches returned when the blood pressure got out of control, and were again relieved when control was re-established, is further evidence against this. Whatever may be said about relief of headache, placebos could hardly be credited with the reversal of fundus and electrocardiographic changes. In patients like Case 28 (Fig. 4) the restoration of vision alone constitutes a very great advance and must make any unpleasantness and inconvenience from treatment a minor consideration to the patient.

The blood-pressure falls shown in Table III may not at first sight appear very dramatic, particularly the diastolic readings; but when account is taken of the fact that these figures represent the estimated lowering in the average blood pressure for the whole day, and moreover that it has been maintained pretty consistently for months on end, it becomes easier to connect the improvement in symptoms and signs with the actual changes in blood pressure. As already mentioned, there is the additional factor of lowering of pressure to normal or near normal levels for one to two hours twice or thrice in the 24 hours, and this may perhaps be the more important of the two considerations. The fact that relief of both headache and cardiac asthma can be correlated with the fall in blood pressure to a more moderate level must subscribe to the rationale of hexamethonium treatment as a practical measure.

The treatment of chronic renal hypertension has been as satisfactory as that of the other groups, and there is no evidence of further impairment of renal function as a result of long-term therapy.

Indication has already been made of cases considered unsuitable for treatment. These are, in summary, (*a*) patients over 60 years, because they run a high risk of thrombotic accidents and also suffer more severely from side-effects; and (*b*) patients under 60 years who have insufficient symptoms or adverse physical signs to justify the disadvantages of treatment.

In a recent review of the pathogenesis of hypertension, Schroeder (1951) draws attention to the evidence that psychoneurogenic factors play an important part in the aetiology, both of essential and of other forms of hypertension; the evidence from this small series that emotional disturbances were not only associated with established hypertension but could actively exacerbate the process in all groups is in agreement with his views. The importance of giving this feature of the disease due consideration in the management has already been pleaded, and one could go further and say that failure of hexamethonium treatment is more likely to be due to psychological than to physical causes.

The finding that "tolerance," so far as the blood pressure was concerned, was not accompanied by similar lessening of parasympathetic effects has suggested that true tolerance to the drug, in the sense of loss of ganglion-blocking power, may not occur to any great degree and that the word is in fact a misnomer. If instead one postulates that for some reason, and in certain cases, the factors maintaining abnormal arteriolar tone are further increased during the evolution of tolerance, the emphasis is shifted from the drug to the disease. It is conceivable that this could be brought about by a large increase in the number of impulses traversing the sympathetic vasomotor pathways (with therapeutic doses ganglion block is probably never complete); or other factors—for example, humoral agents produced in the kidney and elsewhere—may increase in effectiveness. The increase in effect every time the dose is raised (Fig. 6) must be due to blocking of further impulses at ganglia, as this is the only way the drug acts, and therefore favours the former view, but it is possible that humoral factors are also

increased. No evidence has been obtained why this phenomenon is seen to such a varying degree in all clinical groups, or why there is a maximum level of tolerance for a particular patient.

Summary

A study is presented of 39 hypertensive patients on treatment with hexamethonium bromide by subcutaneous injection. The patients were drawn from the complicated-essential, malignant, or renal groups of hypertension, and uncomplicated cases were not included.

Details of treatment routine and general management are given, as it is felt that these are of great importance in the achievement of successful results.

Five patients died whilst on treatment and it was discontinued for various reasons in six others, but 28 patients received regular therapy for periods varying between three and fifteen months and were seen at least once a month in the out-patient clinic.

After the development of a very variable amount of tolerance to the drug during the first four to eight weeks, all patients were able to be stabilized on a dose which gave an average blood-pressure level much below that found in the control period. Reduction in mean systolic pressure ranged from 20 to 90 mm. Hg and in mean diastolic pressure from 8 to 40 mm. Hg, and the maximum reductions—for example, one to two hours after an injection—were often twice as great.

Hypertensive headaches (often very severe and incapacitating) were almost completely relieved in 15 out of 19 cases, and lessened in frequency and severity in the other four. Giddiness disappeared and encephalopathic attacks did not recur, except in one instance. Shortness of breath from cardiac causes was generally improved and in several cases there was striking relief from acute cardiac dyspnoea. Diminution in cardiac volume was demonstrated in five out of seven cases after three to six months' treatment, and in seven out of 16 cases electrocardiographic signs of left ventricular hypertrophy were altered towards the normal. Retinopathy was strikingly improved in all severe cases, papilloedema subsiding, and extensive exudates and haemorrhages becoming reabsorbed, with restoration of normal vision after about six months' treatment.

One instance of coronary thrombosis and two major and two minor cerebral vascular accidents occurred during treatment, but in two of the latter the blood pressure was high at the time. No evidence of increased damage was found among patients with impaired renal function.

A recent development has been the occurrence of dyspnoea and symmetrical opacities in the lung fields on *x*-ray examination in three patients after fifteen, nine, and seven months' successful treatment. The pathogenesis of this is still obscure.

Side-effects were troublesome in proportion to the size of the dose and thus most severe in the cases developing a higher degree of "tolerance." The problem of "tolerance" is discussed and some suggestions are made regarding its nature.

I should like to thank Professor J. McMichael for his help and advice in carrying out this study and in preparing the paper, also Dr. W. D. M. Paton for estimating the plasma levels, Dr. J. F. Goodwin for the E.C.G. reports, and Dr. R. E. Steiner for the cardiac volume estimations. My thanks are also due to Messrs. May and Baker Ltd. for supplies of the drug, for technical assistance, and for a grant towards the expenses of this investigation.

REFERENCES

Bechgaard, P., Iversen, T., and Nielson, A. L. (1951). *Ugeskr. Læg.*, **113**, 1335.
Blainey, J. D. (1952). *Lancet*, **1**, 993.
Campbell, A. J. M., Graham, J. G., and Maxwell, R. D. H. (1952). *British Medical Journal*, **1**, 251.
—— and Robertson, E. (1950). Ibid., **2**, 804.
Cusack, P. B., and Cusack, A. L. J. (1951). *J. Irish med. Ass.*, **28**, 47.
Freis, E. D., Finnerty, F. A., Schnaper, H. W., and Johnson, R. L. (1952). *Circulation (N.Y.)*, **5**, 20.
Friedman, C. E. (1951). *Acta med. scand.*, **140**, Suppl. 257.
Fullerton, C. W., and Milne, I. G. (1951). *Canad. med. Ass J.*, **65**, 302.
Keith, N. M., Wagener, H. P., and Barker, N. W. (1939). *Amer. J. med. Sci.*, **197**, 332.
Locket, S., Swann, P. G., and Grieve, W. S. M. (1951). *British Medical Journal*, **1**, 778.
—— —— —— and Player, H. P. (1952). Ibid., **1**, 254.
Mackey, W. A., and Shaw, G. B. (1951). Ibid., **2**, 259.
McNally, P. A. (1951). *J. Irish med. Ass.*, **28**, 44.
Morrison B, and Paton, W. D. M. (1953). *British Medical Journal*, **1**, 1299.
Murphy, E. A. (1951). *Lancet*, **2**, 899.
Persson, I. (1951). *Nord. Med.*, **10**, 189.
Saville, S. (1950). *Lancet*, **2**, 358.
Schroeder, H. A. (1951). *Amer. J. Med.*, **10**, 189.
Smirk, F. H., and Alstad, K. S. (1951). *British Medical Journal*, **1**, 1217.

EFFECTS OF HEXAMETHONIUM ON NORMAL INDIVIDUALS IN RELATION TO ITS CONCENTRATION IN THE PLASMA

BY

BRENDA MORRISON, M.D.*

Research Assistant, Department of Medicine, Postgraduate Medical School of London

AND

W. D. M. PATON, B.M.†

National Institute for Medical Research, Mill Hill, London, N.W.7

Since hexamethonium was introduced as a ganglion-blocking agent (Paton and Zaimis, 1948) a number of publications have reported upon its effectiveness in the treatment of hypertension and certain other disorders; but, apart from the original observations of Organe, Paton, and Zaimis (1949) and reports by Arnold and Rosenheim (1949), Arnold, Goetz, and Rosenheim (1949), Burt and Graham (1950), and Grob and Harvey (1950) on the production of hypotension in the recumbent subject with marked fall in blood pressure on standing up, subsequent attention has been directed mainly to the effects of the drug in disease rather than in normal individuals.

Clinical experience with a series of hypertensive patients being treated with hexamethonium at Hammersmith Hospital revealed very early that the reactions were of a most complex nature, and correspondingly difficult to interpret. We felt, therefore, that a further study of the actions of this agent in normal man was necessary.

Clinical Method

Eighteen observations were made on 16 normal young adult volunteers (4 women and 12 men). Since the best clinical results seem to be obtained from regular subcutaneous injections (Smirk and Alstad, 1951), we have given our test doses in this way. After control observations for 20 to 30 minutes, doses between 20 and 100 mg. of a 10% solution of hexamethonium bromide were given subcutaneously. In all but two this was the first dose of hexamethonium. Blood pressure, pulse rates,

*In receipt of a grant from Messrs. May and Baker Ltd.
†Now at University College Hospital Medical School, University Street, London, W.C.1.

pupil changes, and subjective sensations were recorded at suitable intervals. In eight of the subjects estimates of plasma hexamethonium levels were made on venous blood. During the first one to two hours the subjects reclined on a couch or sat, and later proceeded with their ordinary occupations.

For comparison of effects the doses are recalculated as mg./kg. body weight, or as mg./litre of extracellular fluid (taken to be 20% of body weight; Gamble, 1949).

Blood pressure was recorded by the auscultatory method with a diaphragm stethoscope strapped to the

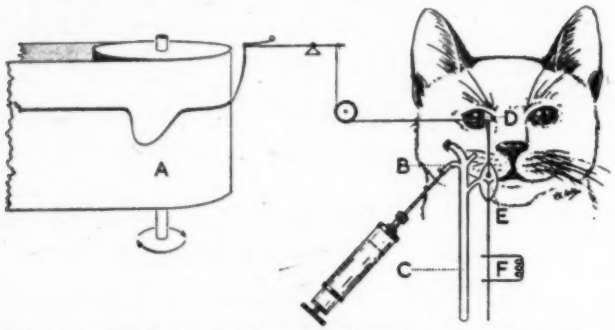


FIG. 1.—Diagram of the preparation used in the assay of hexamethonium. A=Smoked drum. B=Cannula in external carotid artery. C=Carotid trunk. D=Suture through nictitating membrane. E=Electrodes on sympathetic trunk.

arm over the brachial artery. Readings were taken in three positions—standing erect, sitting upright on the edge of the couch, and semi-recumbent on the couch with legs horizontal. Owing to the often-continued fall of blood pressure on maintaining the upright posture, an arbitrary standard time was allowed to elapse before the pressure was measured; for the first three tests (Table IV) the reading was taken in 60 seconds, but thereafter it was changed to 30 seconds, which was found to be less unpleasant for the subject. During an acute postural fall in blood pressure the sounds at times become very soft and difficult to hear; the systolic can be checked by palpation, but some of the diastolic readings must be of doubtful accuracy.

Pulse rates were counted simultaneously with or immediately following the blood-pressure measurements.

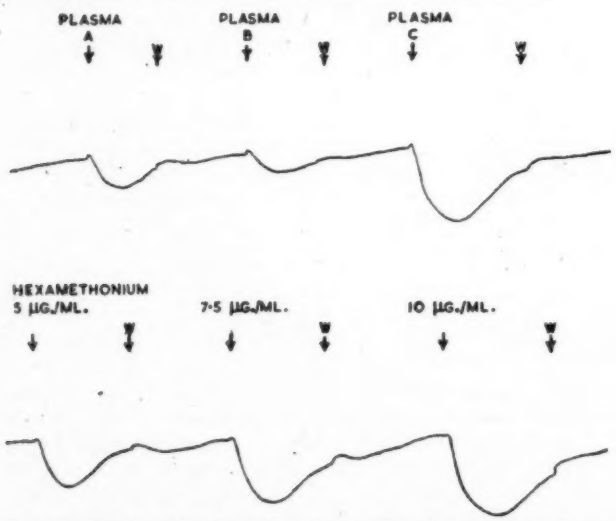


FIG. 2.—Tracings showing relaxation of the nictitating membrane when ganglionic transmission is interfered with following close arterial injection of samples of plasma containing hexamethonium (above) and of standard solutions of hexamethonium in saline (below). Estimations are made by direct comparisons of tracings. Arrows mark injections; W=saline wash-in.

Subjective effects were recorded at each point, and a note made on dryness of the mouth, blurring of near vision, and sleepiness. Objectively, pallor, conjunctival injection, and somnolence were looked for.

Pupil Changes.—Three different aspects of pupillary function were examined: resting size of pupil (so far as possible in the same lighting as the control observations), reaction to light, and contraction on accommodation.

Assay of Hexamethonium in Plasma

We have made use of a bio-assay method for estimation of plasma levels, introduced by one of us (W. D. M. P.), but it will be readily understood that this method is too difficult and too time-consuming to be used as a routine procedure in the control of therapy.

Blood samples were taken into dry all-glass syringes and heparinized immediately. The plasma was separated within an hour or two and stored in the refrigerator until assayed.

The concentration of hexamethonium in each sample was determined by comparing its effect with that of a standard concentration of hexamethonium on close-arterial injection into the continuously stimulated cat's superior cervical sympathetic ganglion. The ganglion was excited by tetanization of the pre-ganglionic cervical sympathetic trunk at rates between 15 and 50 shocks per second, and the activity of the ganglion was measured

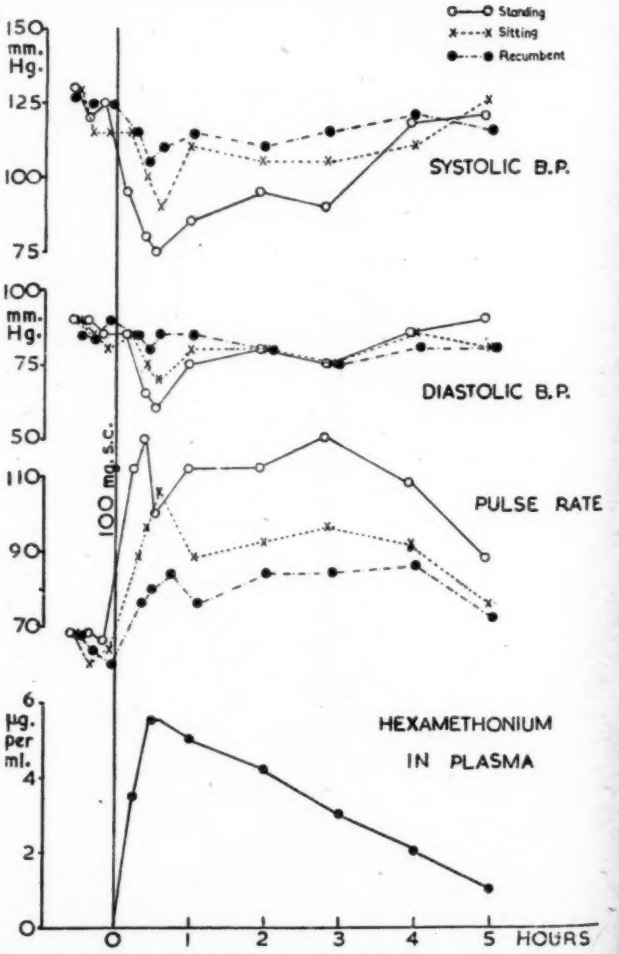


FIG. 3.—Graph of systolic and diastolic pressures and pulse rates, in standing, sitting, and recumbent postures, and levels of hexamethonium in the plasma, following a subcutaneous dose of 100 mg. in a normal individual.

TABLE I.—*Effects of 100 mg. Hexamethonium Given Subcutaneously to a Normal Individual*

Time	Blood Pressure (Pulse Rate)			Concn. of Hexameth. in plasma μg/ml.	Faintness, etc.	Other Sensations	Dry Mouth	Blurred Vision	Increase in Pupil Size		Reaction to Light		Accommodation		Other Observations
	Standing	Sitting	Recumbent						R.	L.	R.	L.	R.	L.	
− 30 min.	130/90 (68)	130/90 (68)	127/85 (68)												
− 20 ,,	120/90 (68)	115/85 (64)	125/85 (64)		—	—	−	−	−	−	+	+	+	+	
− 5 ,,	125/85 (72)	115/80 (64)	125/90 (60)												
Zero	100 mg. hexamethonium bromide (10% solution)														
+ 10 min.	95/85 (112)	115/85 (112)	115/85 (76)		Sl. faint on standing	—	−	−	−	−	+	+	+	+	Not sleepy. Pink face. Some conjunctival injection (+) Yawning. Hand cool
+ 15 ,,				3·6											
+ 25 ,,	80/65 (120)	100/75 (96)	105/80 (80)	·	More faint on standing	—	+	−	+	+	+	+	(+)	(+)	
+ 37 ,,	75/60 (100)	90/70 (100)	110/85	5·5	Faint+ on standing	Dull posterior headache on standing	+	−	+	+	++	++	(+)	(+)	Pallor ++. Hand warmer
+1 hr. 5 ,,	85/75 (112)	110/80 (88)	115/85 (76)	5·0	Faint+ on standing	—	+	−	+	+	+	+	(+)	(+)	Pallor less, but +
+1 ,, 55 ,,	95/80 (112)	105/80 (92)	115/80 (84)	4·5	—	—	−	Dazzled outside	+	+	+	+	(+)	(+)	Still pale
+2 ,, 47 ,,	90/75 (120)	105/75 (96)	110/75 (84)	3·0	—	—	+	−	+	+	+	+	+	+	,, ,,
+3 ,, 55 ,,	115/85 (108)	110/85 (92)	120/80 (86)	2·0	—	Heaviness in head	+	−	−	−	++	++	+	+	,, ,,
+4 ,, 52 ,,	120/90 (88)	125/80 (76)	115/80 (72)	1·0	—	—	−	−	−	−	+	+	+	+	—

by recording the contraction of the nictitating membrane on a smoked drum (Fig. 1). Interference with ganglionic transmission causes a relaxation of the sustained contraction (Fig. 2). The results of the assay are given as micrograms of hexamethonium bromide per millilitre of plasma.

Clinical Data

(a) Example

Fig. 3 and Table I show the typical action of a subcutaneous dose (100 mg.). The most prominent effect was on the standing systolic blood pressure; the time course is seen in the figure. The sitting and recumbent pressures showed similar but less pronounced falls. The changes in the diastolic pressures were in the same direction in each instance, but smaller. Concurrently with the pressure changes there was an acceleration of the pulse, most noticeable on standing and reaching its highest value (plus 50 beats a minute) 30 minutes after the injection. After 10 minutes the subject noticed slight faintness on standing, and this became more severe at 25 and 35 minutes; thereafter it rapidly diminished, and was not complained of after 65 minutes. Pallor of the face was noted after 30 minutes and took about three hours to disappear. At the same time he remarked on a heavy feeling in the head and became slightly sleepy. He did not notice any disturbance of vision, except for some dazzle on going out into bright sunshine. Objectively, however, the pupils were noticeably dilated between 25 minutes and three hours after the injection, and for most of this time contraction on accommodation was diminished, though the reaction to light was never much affected. Dryness of the mouth was complained of after 25 minutes, and persisted for four hours.

Simultaneously with these events, hexamethonium appeared in the plasma, having a concentration of 3.6 μg. per ml. in 15 minutes, reaching a maximum of 5.5 μg. in 37 minutes, and falling thereafter to 1 μg. after five hours.

(b) Grouped Results

1. *Systolic Blood Pressure.*—Effects similar to those just described, but with considerable variation in magnitude, were seen in all subjects. The average blood-pressure fall in the standing posture was 30%, while in the sitting posture it was 19.5% and recumbent it was 9.5%.

Fig. 4 shows the maximal falls expressed as a percentage of the control blood pressure, plotted against the dose in milligrams per litre of extracellular fluid. It will be seen that there is only a broad correlation between the dose and the effect on the blood pressure. Two subjects (A and B) appeared to be exceptionally sensitive to the drug; it may be significant that one of these—A—failed to show the usual tachycardia on standing up, her pulse rate falling to 56 a minute, with other appearances rather like a vaso-vagal attack, which were relieved by lying flat. The other—B—felt only slight giddiness with a systolic pressure of 55 mm. Hg, but he too failed to develop tachycardia. The possibility of the occurrence in some individuals of this "vagal" type of reaction would increase considerably the variability of the response; although the incidence of the reaction is low, it can be alarming enough to call for caution in the choice of test dosage.

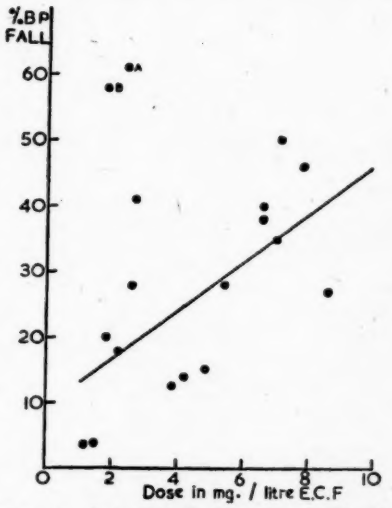


FIG. 4.—Relationship between maximal percentage fall in standing systolic blood pressure and the initial test dose of hexamethonium in 16 normal subjects (18 tests). The regression line is drawn through all points excluding A and B. $r=0.6824$. $P<0.05$.

The maximum fall in the blood pressure was reached in 30 minutes in nine subjects, in 15 minutes in seven subjects, and not until 60 minutes after injection in two; in every case a detectable fall had occurred within 15 minutes. Recovery took place with varying rapidity, being slower with large blood-pressure falls, and was usually well advanced by two hours, though often not complete for three to six hours with larger doses. The time course of the changes in sitting and recumbent pressures was parallel with the above.

2. *Diastolic Blood Pressures.*—These were recorded throughout, but, as already mentioned, their accuracy was doubtful in some cases. In 15 out of 18 cases the same order of percentage fall in diastolic pressures as in the

systolic pressures was seen in the erect position (mean 28%), but in the sitting and recumbent positions the changes were generally insignificant (less than 10 mm. Hg).

3. *Pulse Rate.*—Pulse rates were counted in the first eight subjects, and in all these the rate rose as the blood pressure fell, but the magnitude of the rise showed too great an individual variation to be of use in assessing the effects of the drug. For this reason routine counting of pulse rate was discontinued in the later tests, but tachycardia was usually obvious except in the two cases of bradycardia already referred to.

4. *Subjective Effects.*—Faintness or lightheadedness on standing, sometimes with nausea or sinking feelings in the abdomen, was complained of when the blood pressure fell below 100 mm. Hg in 10 subjects, although these symptoms were not noted in two subjects until the pressure had reached 80 and 55 mm. Hg. In the remaining subjects the blood pressure never fell below 100 mm. Hg and only very transient giddiness, or nothing at all, was noticed. The rapidity of the fall in pressure as well as the actual level reached evidently contributed to the severity of the reaction, and sometimes the faintness passed off whilst the blood pressure was still at a level at which they had previously felt faint.

Four subjects commented on a feeling of warmth in the feet, though none observed it in the hands. One said that his feet felt full, and that they squelched when he stood up. Another experienced a feeling of warmth in the abdomen "like eating a hot meal." Dryness of the mouth of slight or moderate degree was mentioned by 13 subjects.

5. *Objective Effects.*—Pallor of the face was conspicuous in eight subjects during the period of low blood pressure, and occurred mainly in those showing the greater falls. Conjunctival injection was not systematically looked for, but it was sometimes obvious, and one man complained of itching of the eyes. In about half the cases drowsiness was evident to the observer, and was usually confirmed by the subject.

Ocular Changes

Table II summarizes the pupillary changes observed in the 18 tests. The results are arranged in ascending order of dosage. Fig. 5 shows the relationship of ocular changes and plasma concentration of hexamethonium in one of the subjects.

TABLE II.—*Observed Effects of Hexamethonium on Pupillary Function in 18 Normal Individuals, Arranged in Ascending Order of Dose Given. The Figures After the Plus Signs Refer to the Times of Onset and Offset of the Change*

Dose Given (mg. per litre E.C.F.)	Increase in Pupil Size		Interference with Light Reaction		Interference with Accommodation	
	Degree	Duration (Hours)	Degree	Duration (Hours)	Degree	Duration (Hours)
1·2	−		−		−	
1·5	−		−		++	1–?
1·8	−		−		−	
1·85	−		−		−	
2·2	−		−		−	
2·35	−		+	½–?	−	
2·6	−		−		−	
2·7	+	1½ only	+++	½–1½	+	½–1½
3·9	+	½–1	−		−	
4·2	+	½–1½	+	½–1	−	
4·9	+	½–3	+	½–2	+	½–2
5·4	+	1–3	+	½–3	++	½–4
6·5	+	½–2	−		+	½–2
6·5	−		−		+	½–1
7·1	(+)	½–4	++	½–2½	+	1½ only
7·1	+	1–3	++	½–3	++	½–3
7·8	+	½–4	+++	½–4	++	½–4
8·6	+	½–4	+	½–1	++	½–4

Pupil Size.—There was no increase in pupil size at doses less than 2.7 mg. per litre of E.C.F., but above this dose level the pupils always increased in size except in one test. No attempt has been made to assess differences in degree of this change, but the duration was generally longer with the higher doses. The widening of the pupil was never maximal and, moreover, the outline was sometimes irregular, suggesting the paralytic or "dead" pupil rather than the actively dilated pupil of sympathetic stimulation; this probably indicates an interference with both sympathetic and parasympathetic ganglionic transmission.

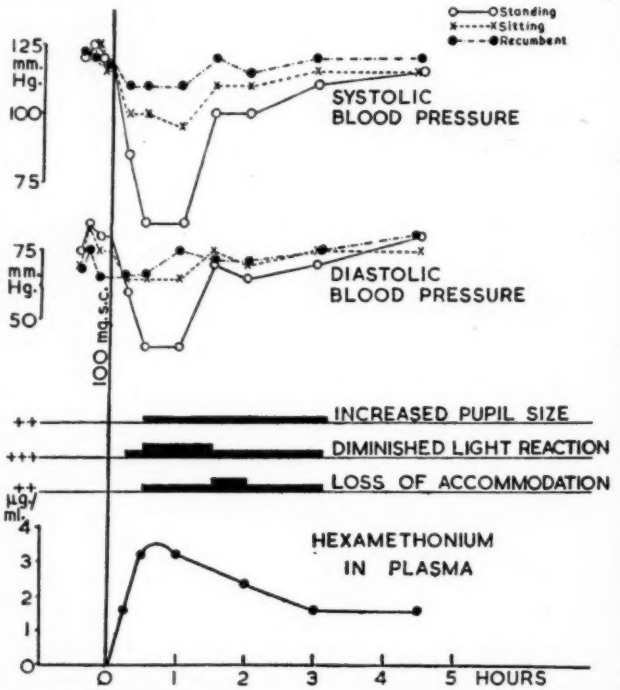


FIG. 5.—Relationship of ocular changes to blood pressure fall and plasma hexamethonium levels in a subject who received 100 mg. subcutaneously.

Interference with Light Reaction.—This was assessed in three grades according to whether the reflex was perceptibly diminished (+), very sluggish (++), or abolished (+++). No interference was seen with doses below 2.35 mg. per litre; above this level there was a rather variable effect: four cases showed no change at 2.6, 3.9, 6.5, and 6.5 mg., but one at 2.7 mg. showed complete paralysis. In the remainder there was a general increase in the degree and duration of reduction of the light reflex in proportion to the dose. When the light reaction was partially paralysed the contraction was often ill-sustained, although the pupil did not undergo the repeated fluctuations of true hippus. Poorly sustained contraction may sometimes be seen in normal pupils, but is much commoner under the influence of hexamethonium.

Interference with Accommodation Reaction.—No change in accommodation was seen below 4.9 mg. per litre, with the exceptions of an unusually late effect in a one-eyed subject at 1.5 mg., and a slight very transient effect in a second subject at 2.7 mg. With doses above 4.9 mg. per litre there was consistent interference with or loss of accommodation for periods between one and four hours. As this reaction has a considerable voluntary component it is possible that the slighter degrees of ganglion block by hexamethonium may be compensated by increased effort on the part of the subject. The convergence of the eyeballs is quite unaffected.

Concentration of Hexamethonium in the Plasma

Fig. 3 showed a typical graph of the rise and fall of concentration of hexamethonium in the plasma after a subcutaneous injection. To show the extent of variation in shape of such curves they have all been superimposed (Fig. 6). Correction for dose and body weight has not been made, since this would alter the height but not the form of the curves. Fig. 7 shows the standing blood-pressure changes and plasma-concentration curve for the subject who showed the most rapid absorption.

The three phases of the curve—that is, the rise, the peak value, and the subsequent fall—considered pharmaco-

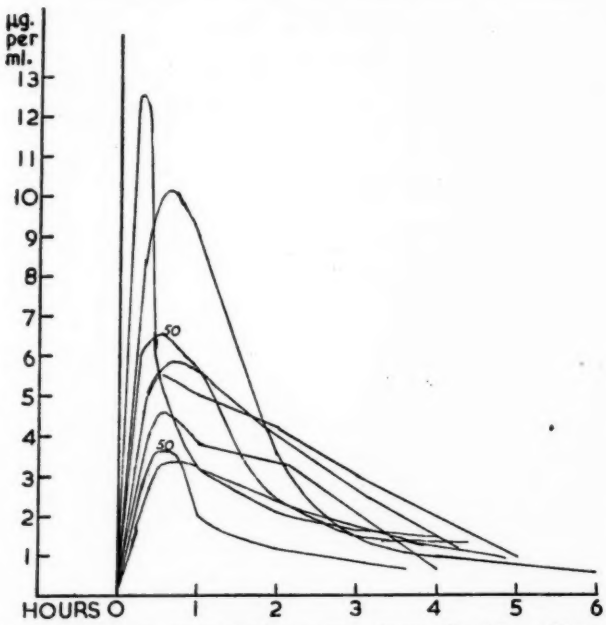


FIG. 6.—Plasma concentration curves from all eight subjects, superimposed to show differences in shape (not adjusted for body weight. Two received 50 mg. and six received 100 mg.).

logically, correspond to the three factors determining the plasma levels—that is, the rate of absorption, the volume of body fluid in which the hexamethonium is dissolved, and its rate of excretion by the kidney. These three aspects are considered in turn.

Rate of Absorption.—The rate of absorption can be estimated from the speed with which the peak concentration is approached. The highest value was attained in approximately half an hour or less in all tests. In every test at least half the peak value, and often much more, was reached in 15 minutes. If absorption is an exponential process—that is, if equal fractions of the unabsorbed residue are assimilated in equal times—then half the total dose must usually be absorbed in about 15 minutes. A few of the plasma curves have been regular enough to allow an estimate of the rate of excretion to be made, and hence an estimate of the amount left unabsorbed at various times. When this is done the absorption — that is, the fall in the amount still unabsorbed — follows the postulated exponential course. These considerations imply that absorption should be seven-eighths complete within about one hour in most individuals.

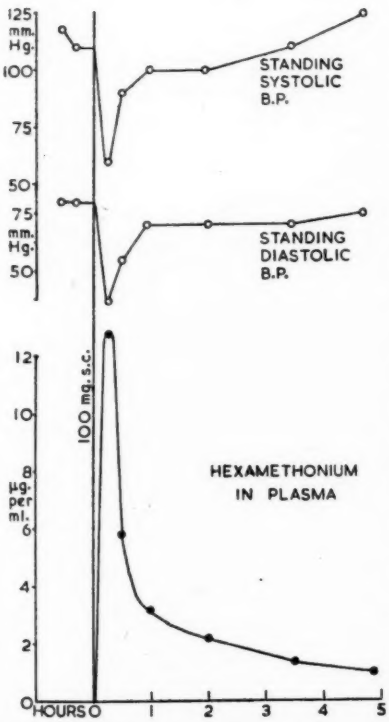


FIG. 7.—Plasma concentration curve and standing blood pressures in the subject who showed the most rapid absorption of hexamethonium after subcutaneous injection.

Distribution in the Body. — The peak plasma values in each test are given in Table III. They correspond in magnitude to a distribution of the drug in a volume equivalent to between 10 and 41% of body weight. Of these values four lie within the 15–25% range (which appear to be the extreme values for extracellular fluid given in the literature), two lie above this (28% and 41%), and two below it (10.3% and 12.2%). The range and average (23.1%) of these figures suggest that hexamethonium is in fact dissolving in extracellular water. Incomplete distribution outside the vascular compartment and a variable rate of excretion would readily account for individual discrepancies.

TABLE III.—*Peak Plasma Levels Found in Each Subject with Dose of Hexamethonium Injected and the Weight of the Subject. Columns 5 and 6 Show the Estimated Volume of Solution of the Drug at the Peak Times in Litres and as a Percentage of Body Weight Respectively*

Subject No.	Dose Given	Wt. of Subject	Peak Plasma Level	Calc. Vol.	% of Body Weight
1	100 mg.	58 kg.	10 mg./litre	10 litres	17·2
2	100 ,,	92 ,,	4·5 ,,	22 ,,	24·2
3	100 ,,	76 ,,	5·5 ,,	18·2 ,,	23·9
4	50 ,,	64 ,,	6·4 ,,	7·8 ,,	12·2
5	100 ,,	76 ,,	12·8 ,,	7·8 ,,	10·3
6	100 ,,	70 ,,	8·0 ,,	12·5 ,,	17·9
7	100 ,,	70 ,,	3·5 ,,	28·6 ,,	40·9
8	50 ,,	51 ,,	3·5 ,,	14·3 ,,	28·0

Excretion.—It is already known that about 90% of a parenterally administered dose can be recovered from the urine during the subsequent 12 hours (Zaimis, 1950; Milne and Oleesky, 1951; Wien and Mason, 1951; Harington, unpublished). We have calculated the expected clearance of hexamethonium by simple filtration in our subjects from the plasma-concentration curves, assuming that the glomerular filtration rate (G.F.R.) remains normal under the influence of the drug (Moyer and Mills, 1953) and has therefore a mean value of 125 ml. per minute (s.d.=25 ml. per minute). The periods of observation were four to six hours, by which time the plasma concentrations had sunk in five subjects to 1 µg. per ml. or less, and in the remainder were below 1.6 µg. per ml.

In Table IV the expected amounts excreted have been calculated first from the mean G.F.R. and secondly from the upper and lower limits of the G.F.R. (taking ± twice the standard deviation for this purpose). Although the dose given differs in some instances considerably from the former calculated value, in one case only does it fail to fall within the range of the expected excretion. These results are compatible with the excretion of hexamethonium by simple filtration without tubular excretion or reabsorption—that is, like inulin—and in this our findings agree with those of Young, de Wardener, and Miles (1951), who made a direct comparison of inulin and hexamethonium clearances.

TABLE IV.—*Expected Amounts of Hexamethonium Excreted Over Four to Six Hours by Simple Glomerular Filtration, as Calculated from Plasma-concentration Curves and Normal Range of Glomerular Filtration Rates*

Subject	Expected Total Excreted (mg.)		Dose Injected (mg.)
	From Mean G.F.R.	From 2×S.D. Range of G.F.R.	
1	143	86–200	100
2	66	40–93	100
3	86	52–121	100
4	100	60–140	50
5	99	59–138	100
6	150	90–210	100
7	74	44–103	100
8	44	26–61	50
Average	95		88

Correlation of Clinical Data with the Concentration of Hexamethonium in the Plasma

Blood Pressure

It has already been mentioned that the degree of reduction of blood pressure runs parallel to the rise and fall of

hexamethonium in the plasma. In Figs. 3, 5, and 7 this parallelism can be seen for three types of curve, and the same relationship was found in the remaining tests. The maximum blood-pressure fall always coincided within a few minutes with the peak plasma concentration, and the blood pressure returned to the control value when the plasma concentration fell to about 2 μg. per ml. (1–3.5 μg.). In no case was there a detectable fall in blood pressure with a plasma concentration of less than 1 μg. per ml. No observations of blood pressure were made during the first 10 minutes after injection, so that the plasma levels at the onset of the blood-pressure falls are not accurately known.

To reduce the standing systolic blood pressure below 100 mm. Hg (which was the usual level at which faintness occurred in normal subjects), plasma concentrations varying from 2.5 to 7.8 μg. per ml. were necessary in different individuals.

The variability of these responses led to a more detailed analysis of the individual tests. In Fig. 8 all the plasma concentration values obtained in each of five subjects are

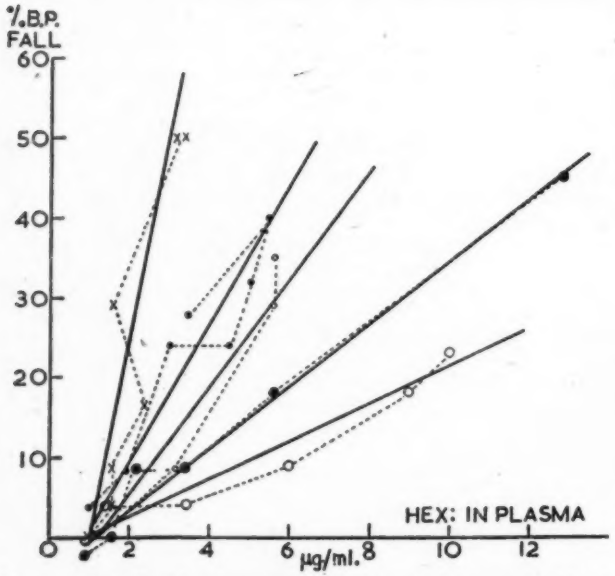


FIG. 8.—Relationship of percentage fall in standing systolic blood pressure to different plasma levels of hexamethonium in five subjects. Although the relationship is a linear one for each individual, the sensitivity of the different individuals is very variable.

plotted against the corresponding reductions in standing systolic pressure, making no distinction between the rising and falling phases of the curves. This graph illustrates the point made earlier, that a definite threshold value of hexamethonium in the plasma (about 1 μg. per ml.) is necessary before detectable changes in blood pressure occur. For each individual there is a surprisingly close relationship between the plasma concentration and the effects on the blood pressure; this relationship is unusual in that the effect of the drug varies directly with its concentration in the body rather than with the logarithm of its concentration. This regular relation for an individual subject contrasts strongly with a considerable variation in sensitivity between different subjects, and the latter accounts for the wide scatter in response to a test dose already shown for the whole group (Fig. 4).

It is possible to obtain an index of sensitivity for each individual from the slopes of lines shown in Fig. 8; this index is expressed as fall in blood pressure per unit concentration of hexamethonium in plasma. For the five subjects of Fig. 8 this index is respectively 3, 4.5, 8.5, 11, and 25% fall in standing systolic B.P. for each μg. per ml. It follows from this that there exists in normal individuals a basic variation in sensitivity to hexamethonium over at least an eightfold range, quite apart from differences in absorption, distribution, and excretion, or liability to "vagal" attacks of the kind mentioned earlier.

Dryness of the Mouth

This effect of hexamethonium was noticed by six of the subjects at minimum plasma levels of 2, 2, 3, 3.5, 4, and 8 μg. per ml. In the other two subjects it was not present, but in neither of these did the plasma concentration exceed 3.5 μg. per ml.

Ocular Changes

Table II showed the relationship between dose of hexamethonium and interference with pupillary function. In the eight subjects in whom plasma levels of hexamethonium were estimated a more direct comparison of these changes with concentration of the drug can be made.

Increased pupil size was seen with plasma levels above 1, 1, 1, 1.5, 2, 4, and 5.5 μg. per ml. In one subject no increase was seen, although the peak plasma value was 12.8 μg. per ml.

Interference with light reaction was observed in five subjects at threshold values of 1.5, 1.5, 2, 5, and 8 μg. per ml., but failed to occur in three subjects in which peak plasma levels of 5.5, 6.4, and 12.8 μg. per ml. were reached.

Interference with accommodation was observed in seven subjects at plasma levels above 1, 1, 1.5, 1.5, 3, 4, and 5.5 μg. per ml., but not in the eighth subject, whose peak value was 6.4 μg. per ml.

These results are ranked in order of magnitude, as the three pupillary functions seem to be affected independently of each other in the individual subject; on the other hand, the ranges of thresholds for interference with the three functions are similar.

Discussion

The effects of hexamethonium in normal man have been examined in some detail because this substance may be regarded as a prototype of the drugs which, by paralysing autonomic ganglia, are likely to prove useful in the treatment of hypertension and certain other disorders.

In this study no effects of hexamethonium have come to light which cannot be explained on the basis of blocking of either sympathetic or parasympathetic ganglia, with the possible exception of the drowsiness which occurs in many subjects.

Under the conditions of this study and with initial test doses of 25–100 mg., the ganglia which appear to be most prominently affected are those of the sympathetic chain, since the fall of blood pressure with postural accentuation has been the earliest and most constant finding. After these blood-pressure effects the detectable actions of next importance are on the ciliary and salivary ganglia. With the doses used there was no subjective evidence of significant interference with intestinal or bladder autonomic nerve supply.

It is interesting to find that in a particular subject the pupillary resting tone, reaction to light, and contraction on accommodation may be affected to different degrees by hexamethonium, and also that the order of onset of interference with these functions may vary with the individual. Such differences in behaviour between ganglia, and also apparently between different pathways within the same ganglion, are already known in the response to nicotine, hexamethonium, and other substances in animals. The interest of these variations lies in the hope they offer that other ganglion-blocking agents may be found which will have an action directed more specifically towards ganglion pathways subserving different functions—for example, those controlling vasomotor tone.

Postural hypotension with hexamethonium has been recognized from the earliest reports, and all our subjects showed this phenomenon. Although the maximum blood-pressure fall was always seen in the standing position, the falls in the sitting and recumbent positions ran a parallel time course in each case. When the average maximal depressions in blood pressure for the whole group are compared, the falls in the sitting positions are about half and those in the recumbent positions are about one-third of those in the

standing position. It is interesting that the hypotension in the sitting position is not greater, and, in fact, that the blood pressure rises promptly on sitting down.

A great deal of attention has been paid in these experiments to recording blood pressure in the erect posture, using a fixed time limit as described. Standing systolic readings have proved to be a convenient measure of the total effect of the drug on the blood pressure, since the changes in these readings are bigger in proportion to the errors of technique than in the sitting or recumbent positions, and, moreover, they provide an important measure of the maximum effect of the drug.

The distribution of hexamethonium in the body and its excretion at a rate comparable to that of inulin correspond to its quaternary nature. Bases in general penetrate the cell membrane only in the un-ionized form (Höber, 1945). Salts of quaternary nitrogen when in solution are completely ionized, and hence can only traverse the cell membranes very slowly. Accordingly they must lead an extracellular existence in the body, and should be unable to be either secreted or reabsorbed by the kidney tubules.

The indication from clinical data (Fig. 4) that normal subjects vary considerably in their response to hexamethonium was borne out and further elucidated by the plasma-concentration curves. Part of this variation is obviously due to the differences in absorption, distribution, and excretion already described; but the main variation, and one that cannot be eliminated by changing the route of administration, lies in the actual response of different subjects to the same concentration of the drug in the plasma (Fig. 6). The immediate practical application is that it is not safe to give initial doses of more than about 30–40 mg. subcutaneously to ambulant patients, even though this dose may produce little response in many individuals.

The somewhat unexpected finding of a linear rather than a logarithmic relationship between the plasma concentration and the effect on the blood pressure has some practical importance in addition to its theoretical interest; when treating patients for hypertension the dose should not be increased too rapidly. Increments of not more than 25–50 mg. should be used according to the individual patient's sensitivity.

The manner in which these findings in normal subjects may be applied to hypertensive patients under treatment is being studied and will be reported later.

Summary

A detailed study of the clinical effects of a subcutaneous test dose of hexamethonium in 16 normal individuals is reported, and plasma-concentration curves are described in eight of these.

No effects have been observed which could not be attributed to ganglionic block, with the possible exception of drowsiness.

Calculations from the concentration–time curves of hexamethonium in the plasma indicate that the drug is evenly distributed through the extracellular fluid, and they are compatible with its excretion by glomerular filtration.

Considerable variation in the response of different individuals to hexamethonium has been shown to occur, in relation both to the dose given per kilogram of body weight and to plasma levels. The thresholds for reduction of blood pressure, for elevation of pulse rate, and for interference with three separate pupillary functions varied from subject to subject, independently of each other.

For a given individual there was a close linear relationship between the plasma concentration and the degree of blood-pressure reduction.

We should like to thank Professor J. McMichael for his advice and helpful criticism in the carrying out of this work.

References

Arnold, P., Goetz, R. H., and Rosenheim, M. L. (1949). *Lancet*, **2**, 408.
—— and Rosenheim, M. L. (1949). Ibid., **2**, 321.
Burt, C. C., and Graham, A. J. P. (1950). *British Medical Journal*, **1**, 455.
Gamble, J. L. (1949). *Chemical Anatomy, Physiology, and Pathology of Extracellular Fluid*. Harvard Univ. Press, Cambridge, Mass.
Grob, D., and Harvey, A. M. (1950). *Bull. Johns Hopk. Hosp.*, **87**, 616.
Höber, R. (1945). *Physical Chemistry of Cells and Tissues*. Churchill, London.
Milne, G. E., and Oleesky, S. (1951). *Lancet*, **1**, 889.
Moyer, J. H., and Mills, L. C. (1953). *J. Clin. Invest.*, **32**, 172.
Organe, G., Paton, W. D. M., and Zaimis, E. J. (1949). *Lancet*, **1**, 21.
Paton, W. D. M., and Zaimis, E. J. (1948). *Nature, Lond.*, **162**, 810.
Smirk, F. H., and Alstad, K. S (1951). *British Medical Journal*, **1**, 1217.
Wien, R., and Mason, D. F. J. (1951). *Brit. J. Pharmacol.*, **6**, 611.
Young, I. M., de Wardener, H. E., and Miles, B. E. (1951). *British Medical Journal*, **2**, 1500.
Zaimis, E. J. (1950). *Brit. J. Pharmacol.*, **5**, 424.

FARMER'S LUNG

BY

T. C. STUDDERT, M.D., M.R.C.P.
Assistant Physician, Cumberland Infirmary, Carlisle

A condition conveniently named "farmer's lung," readily recognized clinically and radiologically, has been reported in the medical literature in the past, but some confusion has existed about the causal mechanism and the natural history of the disease. The purpose of this paper is to review the literature, to present a small series of cases, and to advance a theory to explain its aetiology.

Review of the Literature

Campbell (1932) presented case histories of a small number of agricultural workers from North Westmorland who were referred to his clinic as possible cases of tuberculosis. All gave a history of sudden onset of intense breathlessness, cough, slight fever, and, in some, loss of weight following exposure to dust from mouldy hay.

The clinical picture in each case was of a distressed, blue, dyspnoeic patient, and clinical examination revealed widespread crepitations throughout the lungs. Radiologically the picture was of increased lung markings with superimposed soft shadows. Spontaneous recovery in one to two months occurred, but some residual fibrosis and emphysema were noted in a few cases. One patient subsequently died, but necropsy showed coincidental cystic disease of the lungs (Campbell, 1950—personal communication). Through the kindness of Dr. Campbell it has been possible to study the *x*-ray films of one of his original cases followed up for 18 years. Some fibrosis and emphysema were the only findings.

Fawcitt (1936, 1938, 1940) studied the condition in West Cumberland and concluded from culture of similar moulds in the sputum and the hay dust that this was a fungous infection of the bronchi and lungs. He used the term "bronchomycosis feniseciorum" and advocated treatment with iodides. It should be stated that the condition described by Campbell (1932) and that of many of Fawcitt's (1938) cases were clearly not true aspergillosis, which is a distinct and well described clinical entity (Sayers and Meriwether, 1932; Smith, 1947). "Thresher's lungs," if aspergillosis is excluded, is an analogous condition in workers exposed to mouldy corn dust, and presents a picture identical to farmer's lung.

Duncan (1945), in a review of fungous diseases, stated that he had received specimens of sputum relating to this disorder from physicians in rural areas stretching from Cumberland to Devon. He cultured many varieties of

fungus from the specimens, but came to the conclusion that this only indicated exposure of the patient to dust containing the relevant spores, and was no criterion of actual infection. He put forward a theory that the symptoms could be explained by an irritation of the lungs from a fine vegetable dust resulting from breakdown of hay fibres by the fungus, and that the disease was comparable to byssinosis.

The *Lancet* (1948) made a plea for further investigation of this and allied conditions, but the *British Medical Journal* (1950) still quoted the fungus theory and recommended iodide treatment.

Distribution and Frequency

The distribution of reported cases is of interest, as the condition appears to be most common in the North-West of England. Possible reasons for this are the high rainfall at hay-time, and primitive methods of harvesting and storage in closed barns. The old threshing barns with fixed installation are still in use, and many farmers remember cases of sudden death following acute chest symptoms in men working all day in some of the old ill-ventilated barns. Threshing engineers and farmers are familiar with the clinical picture of farmer's lung, and refer to being "moulded." The white irritant dust set up when mouldy hay is disturbed is locally referred to as "stour" and treated with respect. "Broken-windedness" in horses is attributed to the feeding of mouldy hay, and is largely prevented by dampening the hay before feeding.

The rarity of the disease in hospital practice was in contrast with the evidence of the farmers, and so it was decided to circularize the practitioners of the area asking for information. The response was excellent, and a clearer picture of its true distribution emerged. Family practitioners in the smaller market towns were quite conversant with both the clinical picture and the natural history of the disease, and could advise the farmer suffering from these symptoms of his probable progress and time off work. As there was no problem in their minds, these doctors did not, as a rule, refer their patients to hospital unless radiological confirmation was sought. It was from conversation with Dr. A. G. Abraham, of Cockermouth, Dr. E. Braithwaite, of Egremont, and Dr. H. P. Nelson, of Brampton, that many valuable facts about the disease were learned.

The present series consists of six cases—confirmed radiologically, and six probable cases—radiologically inconclusive.

Proved Cases

Case 1.—A farm labourer aged 22 had no history of chest trouble until January–March, 1950, when he had bouts of mild bronchitis, often following exposure to hay dust. On August 4 he worked all day stacking poor-quality hay from which there was a lot of white irritant dust. By evening he was distressed, coughing, and breathless. After a rigor he started to sweat, felt very feverish, and vomited. After six days of persistent breathlessness and distress, despite sulphonamide therapy, he was admitted to hospital. The clinical picture was that of a cyanosed, breathless, and ill man. Clubbing of the fingers was not noted, and chest examination revealed generalized fine crepitations, without any localized dullness or signs of consolidation. There was no evidence of cardiac enlargement or failure. An *x*-ray film of the chest taken on August 10 showed: "An overall opacity of both lung fields, excluding the apices and costophrenic angles, with the greatest density in the lower mid-fields, and extending to the extreme periphery of the lung. In the areas of least involvement the opacity fades to a fine granular mottling. . . . The detail of the lung roots is almost completely obliterated. There is no pleural fluid, and no cardiac enlargement" (Figs. 1 and 2). The sputum was cultured and yielded a good growth of *Bacillus subtilis*, but no fungi. A differential white blood cell count showed

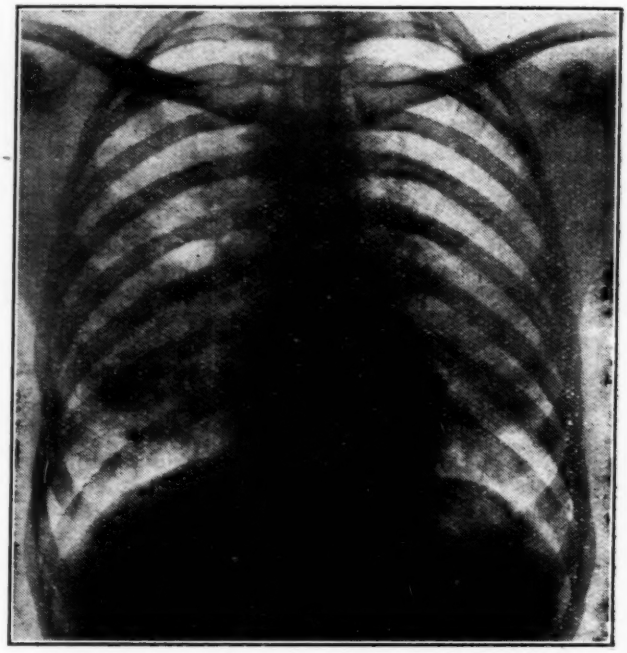


FIG. 1.—Case 1. *X*-ray film taken on August 10, 1950.

no eosinophilia. Dust from the barn grew *B. subtilis* and various aspergilli. Skin tests showed no specific reaction to dust extracts or mould cultures. Treatment with mepyramine maleate, 0.1 g. thrice daily, was instituted without obvious effect, but the patient gradually improved, and a follow-up *x*-ray film taken four months later showed normal lung fields.

Case 2.—A married woman aged 47 was admitted to hospital on December 17, 1947. She had been quite healthy until two weeks before admission, when she and her son (Case 3) swept out a closed barn in preparation for the storage of some newly threshed corn. She became very breathless that night, and symptoms persisted until she was admitted. She complained of slight fever, a dry cough, and intense breathlessness out of proportion to her other symptoms. On admission her temperature was 100.4° F. (38° C.), pulse 100, and respirations 56. There were widespread fine crepitations, maximal at the left apex, and an *x*-ray film showed: "An opacity mainly of the left upper zone, but, in lesser degree, of both lower zones. As in Case 1, the opacity extends to the periphery of the lung fields, and fades to fine mottling. The root shadows also show loss of detail, particularly the left." The white blood count was 7,200 per c.mm., with 4% eosinophilia, the sputum was

FIG. 2.—Enlarged view of part of Fig. 1.

mucopurulent, but yielded no significant organisms or fungi. She was treated with diphenhydramine hydrochloride, and improvement was gradual. On January 1, 1948, she was discharged home and continued to do well.

Case 3.—The son of Case 2, aged 24, was seen on December 17, 1947, as an out-patient, complaining of cough with mucopurulent sputum, nausea, night sweats, weight loss, and intense breathlessness. On examination he was cyanosed, with rapid respirations and generalized crepitations. An *x*-ray film of the chest showed : "A complete ground-glass opacity of all zones, extending to the periphery and showing the typical granular mottling in areas of least density. The detail of the root shadows in this case is not obliterated." He was not admitted to hospital, as the condition was recognized and progress at home was uneventful. Follow-up *x*-ray examination in 10 weeks showed almost complete clearing and he was clinically well.

Probable Cases

Case 4.—On October 13, 1950, a man aged 48 swept out his barn containing old corn and oats prior to threshing day. The dust was very irritant and white, and that evening he became breathless and ill. He had never had chest trouble before, but he described himself as being "broken-winded" and ill for the next month, with a dry cough and night sweats. He was referred as a possible case of tuberculosis on December 13, but by then he felt better and clinical and radiological examination revealed only non-specific changes.

Other cases in this group gave a clear history of exposure, but could not be classed as definite without clear radiological confirmation. If practitioners become aware of the condition and refer such cases for early chest *x*-ray examination it is thought that many more cases will come to light.

Clinical Picture

The clinical picture emerges of a non-specific lung irritation which may follow exposure to mouldy vegetable dusts of any type, but mainly contact with poor-quality hay and corn. It may occur during stacking, baling, threshing, forking of hay for animal feeding, or sweeping out a barn in preparation for new grain or hay. Before the severe reaction there may be minor bronchitic episodes following short contact, but this is not invariable, and a clear distinction must be drawn between true farmer's lung and an asthmatic attack following exposure to mouldy dust (see Case 5).

The main feature of the disease is the intense breathlessness and cyanosis which develop within 12 hours of exposure. If symptoms are delayed for more than 24 hours an alternative diagnosis must be considered (see Case 6). The onset is sudden, and may be associated with a rigor, vomiting, a dry cough, and a feeling of suffocation. Irritation of the eyes and nose commonly occurs after contact with the dust, but is not a feature of the disease. The picture at this stage resembles that of a case of acute oedema of the lungs, but there is no evidence of cardiac embarrassment. Widespread fine crepitations are found on examination of the chest, but no localized area of consolidation is detected. Pleurisy is not a feature, and the finding of clinical or radiological evidence of this makes the diagnosis suspect. No case presented with haemoptysis.

The clinical course is fairly constant, and clearing of the radiological picture and physical signs is usual in six to eight weeks. After the first two to three weeks the breathlessness becomes less distressing, but during this period loss of weight and night sweats occur.

After three months the patient appears to be well, but there is a tendency for the condition to recur on re-exposure, and some evidence to suggest that there is a predisposition to the development of some degree of emphysema and fibrosis. No diminution in vital capacity has been noted in the follow-up of the present series over one to five years, but Dr. Campbell's case followed for 18 years showed some fibrosis and emphysema. Dr. W. G. Scott-Harden describes the *radiological picture* in the acute phase as a ground-glass opacity extending to the periphery of the lung fields, and fading to a granular mottling in the areas of least involvement. Although the distribution is most commonly in the mid- and lower-lung fields, with the exclusion of the apices and costophrenic angles, this cannot be taken as invariable. Case 2 illustrates this point, and it is of interest that this patient is the only female in the series and to postulate the relationship between this and the greater frequency of thoracic, as opposed to abdominal, respiration in women. The detail of the root shadows is usually obliterated by the opacity, and return to normal lags behind peripheral clearing. There is no case in the series in which there were dense localized opacities in the lung or evidence of pleurisy, and there was no cardiac enlargement. Clearing is gradual, starting at the periphery, and is usually complete in three months.

Pathological Investigations.—The red blood cells and haemoglobin remain unchanged. The total and differential white-cell counts show no specific change, the maximum eosinophilia being 4% of 7,200 white cells per c.mm. in Case 2. The E.S.R. is normal or slightly raised.

Sputum examination in proved and probable cases yielded a mixed growth of aspergilli in five, penicillium in four, *B. subtilis* in four, and monilia in five cases, in addition to the usual commensals.

Examination of the incriminated dust showed a comparable growth of mixed fungi, but this similarity of cultural characteristics in dust and sputum was only taken as evidence that the patient had recently inhaled the dust, but not in any way as proof of active disease in the bronchi or lungs (see Cases 5 and 6). Assessment of average particle size of the dusts was found to present some difficulty, and is the subject of further investigation, but the impression gained from two samples was that the average diameter of particles was greater than 10 μ.

Animal experiments were carried out by Fawcitt (1938) on a limited scale in an attempt to demonstrate the pathogenicity of spore-laden dust to animals' lungs, without conclusive results.

Skin tests with extracts of the offending dusts and stock solutions of aspergillus, penicillium, and mucor were carried out without obtaining specific reactions in any case.

Differential Diagnosis

1. *Asthma and bronchitis* brought on by contact with mouldy hay or grain is not uncommon in farmers, and seven such cases were seen.

Case 5.—A farm worker aged 62 was seen on September 16, 1950. There was one year's history of dyspnoea and wheezing, made worse by working in a closed barn with poor-quality hay, but no single explosive episode of breathlessness. Examination of the chest revealed signs of chronic bronchitis, with dry rhonchi throughout the lungs, and *x*-ray films confirmed an emphysematous picture without specific changes. Culture of the sputum yielded a good growth of aspergillus and monilia. Dust from the barn showed aspergillus, monilia, and *B. subtilis*. Skin tests with dust extracts showed marked reaction.

The finding of mixed spores in the sputum of this group of cases was invariable and of no significance beyond demonstration of contact with a potential allergen.

2. *Coincidental Pneumonia.*—Most cases were initially treated as pneumonia by the general practitioner, and if any doubt exists this is a wise precaution. It would be a disservice to the farming community if the diagnosis of farmer's lung was made too lightly. The points to be stressed are the dramatic onset within a few hours of exposure, and the absence of signs of consolidation, pleurisy, or haemoptysis in farmer's lung; but confusion may arise in the case of virus pneumonia.

Case 6.—A farmer aged 42, whose previous health had been good, was working a baler and putting through poor-quality hay on February 6, 1952. He had no untoward symp-

toms until 48 hours later, when he felt feverish and breathless, and complained of left-sided chest pain. He was referred after two days as a possible case of farmer's lung. Clinically and radiologically there was evidence of a patchy virus pneumonia, and treatment with chloramphenicol produced a dramatic response. It was the time interval of two days, combined with the patchy radiological appearance, including a basal pleurisy, which made a diagnosis of farmer's lung untenable, despite the finding of aspergillus in the sputum. The risk of converting such a case into true aspergillosis by intensive treatment with chloramphenicol is appreciated.

3. *Miliary tuberculosis* is often clinically suspected, but the mistake can be made only if the history of exposure to dust has not been elicited : also the radiological features are quite different.

4. *Miliary diffuse granulomatous pneumonitis* of unknown aetiology has been reported in men cleaning out a water-tower in Cincinnati which was heavily contaminated with pigeon excreta (Felson *et al.*, 1950). Similar radiological appearances occurred in soldiers clearing out dusty barns in Missouri (Idstrom and Rosenberg, 1944); in soldiers spending some time in a deserted storm cellar in Oklahoma (Cain *et al.*, 1947); and in 21 men who visited a deserted chalk pit in Arkansas (Washburn *et al.*, 1948). All of these cases have been reported as specific entities, but it would appear that, with farmer's lung, they constitute a non-specific lung reaction to a variety of irritants. In each case clinical and radiological clearing occurred in one to twelve months.

5. *Aspergillosis* is an infection of the lungs with pathogenic strains of aspergillus, particularly *A. niger* and *A. fumigatus* Fisher, which may occur in grain handlers. It is a true fungous infection, with active branching hyphae in the sputum, severe illness, and dense infiltration or cavitation of the lungs. There is no spontaneous improvement when the case is removed from the source of infection. It is possible that it may present as a miliary lung picture without serious systemic upset, and proceed to scattered calcification, mainly at the lung bases (Sayers and Meriwether, 1932). Skin tests are variable. Confusion with farmer's lung is unlikely, provided that the finding of the spores of aspergillus in the sputum is taken at its true value.

Treatment

Treatment is largely symptomatic. Fawcitt (1936, 1938, 1940) advocated iodides, but his results differed little from the spontaneous clearing noted in untreated cases. Antihistamine drugs have been used in this series without obvious effect, and antibiotics seem to have a limited value in preventing secondary infection.

As the initial condition has much in common with acute pulmonary oedema, mercurial diuretics may be tried, but in the absence of cardiac enlargement their value is doubtful.

Discussion

The currently quoted view that farmer's lung is an actual fungous infection of the lungs does not bear close examination. The explosive onset, spontaneous clearing, and radiological picture are totally unlike any true fungous disease, and no real evidence has been produced to support this theory. The silica content of vegetable dusts has been analysed with reference to hay dust (Fawcitt, 1936) and dust in cotton mills (Prausnitz, 1936) and found to be negligible, so this may be excluded as a possible factor. That the condition is not simply a severe asthmatic reaction is shown by the distinct clinical and radiological pattern, although it is possible that personal allergy may play a part.

The two remaining theories which explain most aspects of the disease are : (1) irritation of the lungs by fungus spores or some noxious breakdown product; and (2) a mechanical irritation of the lungs by a fine vegetable dust of sufficiently small average particle size to allow deep penetration : this dust may be formed from the action of the fungus on hay fibres, which subsequently disintegrate.

In examining these theories it was considered reasonable to compare the clinical picture of farmer's lung with diseases thought to fall within these two groups, and note points of similarity. Group 1: (*a*) coniosporiosis (Towey *et al.*, 1932); (*b*) weaver's cough (Collis, 1915); and (*c*) possibly the miliary granulomatous lung lesions already mentioned. Group 2: (*a*) byssinosis ("monday fever"); (*b*) bagassosis.

Group 1 (*a*) *Coniosporiosis.*—Towey *et al.* described this as a pneumonitis in lumbermen involving 10% of the men working on one camp as maple-bark strippers. The cork layer of the bark was heavily contaminated with the black spores of *Coniosporium corticale*, which rose in a cloud when the bark was stripped. The men became suddenly ill with severe dyspnoea, cough, cyanosis, and variable fever. Widespread crepitations were noted on examination of the chest, and *x*-ray films showed areas of soft infiltration, tending to spare the apices, with generalized increase of lung markings and reticulation. Spontaneous cure occurred in six to eight weeks, but recurrence of symptoms followed re-exposure. Sputum contained spores of *C. corticale* and mixed monilia, but the latter were non-pathogenic. Animal experiments with the black residue of the spores were not entirely convincing, but the extract caused toxic effects on guinea-pigs' lungs. The authors postulated an irritative lung lesion with local reaction and giant-cell formation, and regarded the two months needed for clinical clearing as a reflection of the time necessary for phagocytosis of the spores to be complete.

Group 1 (*b*) *Weaver's Cough.*—This is a comparable condition occurring in workers handling mildewed cotton, which gives off a white dust of aspergillus, penicillium, and mucor spores.

Group 2 (*a*) *Byssinosis.*—On beginning to work in the card-room of a cotton-mill a transient irritative cough known as "mill fever" used to be very common, but this cleared with continued exposure. After a variable time a certain number of workers developed a tendency to an irritant cough and attacks of breathlessness when returning to the mill after the weekend—hence the name of monday fever. At first the condition wore off on re-exposure, but gradually symptoms spread over the whole week, with severe disability. After a rest of weeks or months they felt quite fit, but return to the mill resulted in an overwhelming recrudescence of symptoms, and eventual disablement from byssinosis (Prausnitz, 1936). *X*-ray films showed non-specific fibrosis and emphysema. The cardroom dust was mainly less than 10 μ in average diameter, and this is regarded as the critical level for deep penetration of particles into the lung (National Silicosis Conference, 1937). In certain conditions the dust contained mixed fungus spores and minute amounts of histamine and a cotton-seed lipid called gossypol. The view generally held (Caminita *et al.*, 1947) is that monday fever and subsequent byssinosis may be due to sensitization of the lung tissues to irritation by proteins in the dust. Haworth and Macdonald (1937) postulated inhalation of histamine+allergen as the cause.

The clinical similarity of coniosporiosis, monday fever, and farmer's lung is striking, but the radiological analogy with byssinosis is less complete. Weaver's cough, however, again appears to be identical wtih farmer's lung, and I have reached the conclusion that all of these conditions represent a lung reaction to a non-specific irritant, probably some foreign protein. There is obviously some degree of personal sensitivity, as there may be only one case of farmer's lung in a group of farm workers handling the same batch of mouldy hay, or one case of coniosporiosis in a group of ten lumbermen. It is felt that no useful purpose is served in attempting to give specific names to the conditions, and that "hay-dust irritation of the lungs" would be an accurate description of some cases, and "corn dust," "cotton dust," or "coniosporium-spore dust" irritation of others.

Comparison of *x*-ray films of farmer's lung with other conditions is instructive, and there is a close resemblance to many diverse diseases, notably the "bats-wing" appearance of uraemic pneumonia. It seems probable that some similar interstitial lung reaction may play a part in the production ot the radiological appearance of these conditions, however dissimilar their aetiological basis.

Further work on the nature of this reaction is necessary before any definite hypothesis can be advanced, and animal experiments on lung reactions to a variety of contaminated dusts may provide the answer. Lung puncture in the acute phase would also be enlightening, but could hardly be justified in a disease without any appreciable mortality. It is felt that, on clinical and radiological grounds alone, there

is enough evidence to support the theory that farmer's lung is not a specific entity, but only a single facet of a similar lung reaction to a variety of irritants.

Summary

A small series of cases of farmer's lung is described, stressing the acute onset and tendency to spontaneous recovery in six to eight weeks.

The close similarity to coniosporiosis, byssinosis, and diffuse granulomatous pneumonitis is stressed.

The theory is put forward that the condition is a non-specific interstitial lung reaction to some material in the fungus-laden dust, rather than a true fungous infection of the lungs.

My thanks are due to Dr. W. G. Scott-Harden for his advice on the radiological aspects of the paper, to Dr. J. M. Campbell for access to *x*-ray films of one of his original cases, to Dr. T. McL. Galloway for permission to include reports of Cases 2 and 3, to Dr. J. S. Faulds and his staff for pathological details, and to the general practitioners of Cumberland and Westmorland.

REFERENCES

British Medical Journal, 1950, **2**, 1184.
Cain, J. C., Devins, E. J., and Downing, J. E. (1947). *Arch. intern. Med.*, **79**, 626.
Caminita, B. H., Baum, W. F., Neal, P. A., and Schneiter, B. (1947). *Publ. Hlth Bull., Wash.*, No. 297.
Campbell, J. M. (1932). *British Medical Journal*, **2**, 1143.
Collis (1915). *Proc. roy. Soc. Med.*, **8** (Epidem. Sect.), 108.
Duncan, J. T. (1945). *British Medical Journal*, **2**, 715.
Fawcitt, R. (1936). *Brit. J. Radiol.*, **9**, 172, 354.
—— (1938). Ibid., **11**, 378.
—— (1940). *Lond. Hosp. Gaz.*, **43**, Clin. Suppl., June, p. iii.
Felson, B., Jones, G. F., and Ulrich, R. P. (1950). *Amer. J. Roentgenol.*, **64**, 740.
Haworth, E., and Macdonald, A. D. (1937). *J. Hyg., Lond.*, **37**, 234.
Idstrom, L. G., and Rosenberg, B. (1944). *Bull. U.S. Army med. Dept.*, No. 81, p. 88.
Lancet (1948). **1**, 252.
National Silicosis Conference (1937). Bull. 13. U.S. Govt. Printing Office.
Prausnitz, C. (1936). M.R.C. Report No. 212 on Byssinosis. H.M.S.O., London.
Sayers, R. R., and Meriwether, F. V. (1932). *Amer. J. Roentgenol.*, **27**, 337.
Smith, D. T. (1947). *Fungus Infections of the Lungs*. Blackwell Sci. Publ., Oxford.
Towey, J. W., Sweany, H. C., and Huron, W. H. (1932). *J. Amer. med. Ass.*, **99**, 453.
Washburn, A. M., Tuohy, J. H., and Davis, E. L. (1948). *Amer. J. publ. Hlth*, **38**, 1521.

INTRACTABLE GASTRIC CRISES RELIEVED BY CHORDOTOMY

BY

G. O. MAYNE, M.B., D.P.H.

Venereologist, Edinburgh Royal Infirmary

Stokes (1944) states that the figures of the American Co-operative Clinical Group show that 45% of patients with tabetic gastric crises are completely relieved by treatment and that an additional 22% are benefited. He adds that standard chemotherapy—that is, neoarsphenamine plus bismuth—is more effective than fever plus tryparsamide or intraspinal methods, and that "the whole surgical field for relief in gastric crises is at best a matter of last and desperate resort." Moore (1941) believes that routine treatment will produce relief of symptoms in 25% of cases, that tryparsamide is of little value, and that the use of fever in addition will relieve a further 25%. Of the 50% of cases thus benefited, however, only 10% may be regarded as cured, and he quotes Keidel's opinion that "if, as rarely occurs, severe attacks are almost continuous, operation may be the only alternative to starvation, morphinism, or suicide." He also states that later experience with penicillin suggests that it is inferior to fever therapy in the treatment of this distressing condition (Moore, 1947).

The following history demonstrates the extent of the problem presented by those cases which do not respond to antisyphilitic treatment and emphasizes the additional fact that neurosyphilitic patients may suffer from unrelated organic intra-abdominal disease.

Case History

A seaman aged 37 was first seen in September, 1947, having had intermittent "stomach pains" and vomiting during the previous nine months. The pains occurred approximately every three weeks, were not related to meals, but were alleviated by alkaline powders. During these periodic episodes the pain was not constantly present, but came in sudden bouts, each lasting about 15 minutes and recurring at frequent though irregular intervals. The pain consisted of a sickening steady ache in the epigastrium, and was accompanied by retching and vomiting. In the previous nine months he had lost 2 st. (12.7 kg.) in weight, and at the time of examination he weighed 8 st. 2 lb. (51.7 kg.). He also complained of shooting pains in both legs of about one year's duration.

On full clinical examination no abnormalities were found except for Argyll Robertson pupils. Serological examination of the blood showed: Wassermann reaction, weak to moderately strong positive (+ to ++); quantitative, five doses of complement fixed; Kahn, strong positive (+++). The cerebrospinal fluid showed: cells, 200 per c.mm.; Wassermann reaction, very weak positive (±); gold sol, 0111000000.

Antisyphilitic treatment was begun with penicillin, but as the condition was strongly suggestive of either peptic ulceration or neoplasm an exploratory laparotomy was performed on October 3 (Professor W. Mercer). No abnormality was found, but the opportunity was taken to remove a small fibrosed appendix.

Treatment with penicillin (100,000 units three-hourly) was continued to a total of 12,000,000 units, and on October 17 he was discharged from hospital. Thereafter he continued to attend for treatment as an out-patient while following his usual occupation of trawlerman, although symptoms recurred at intervals despite continuous treatment with oxophenarsine hydrochloride, tryparsamide, and bismuth. The attacks were the same as those previously described, and lasted sometimes for several days.

Serological examination on June 12, 1948, showed much improvement—blood: Wassermann reaction, weak positive (+); quantitative, four doses of complement fixed; cerebrospinal fluid: cells, 5 per c.mm.; protein, 20 mg. per 100 ml.; globulin, no increase; Wassermann reaction, very weak positive (±); gold sol, 0000000000.

In September, 1948, the patient ceased to attend after having received a total of 12,000,000 units of penicillin, 0.88 g. of oxophenarsine hydrochloride, 39 g. of tryparsamide, and 4.1 g. of bismuth. Later it was learned that in October a recurrence of crises had necessitated his admission to a distant hospital, where he was treated with 16,100,000 units of penicillin, 34 ml. of bismuth tryparsamide, and one session of inductopyrexia—five and a half hours at 104–105° F. (40–40.6° C.).

Between January and June, 1949, he received no treatment, but on June 28 he was again in hospital in a state of extreme misery after further crises. Serological investigation of the blood on June 27 showed quantitative Wassermann reaction ++ (six doses). On July 21 the cerebrospinal fluid showed: cells, 4 per c.mm.; protein, 40 mg. per 100 ml.; globulin, no increase; Wassermann reaction, 0.2 ml. ±; 0.5 ml. +; 1 ml. ++; gold sol, 0000000000. On this occasion treatment consisted of penicillin (100,000 units three-hourly) to a total of 12,000,000 units, malaria (seven rigors), intravenous glucose–saline, pethidine (2 ml. intramuscularly as required). He returned home on September 2, but was readmitted on two further occasions for short periods (October 19 and

November 14) and treated symptomatically with intravenous glucose–saline, pethidine, and morphine.

In February, 1950, he was again in hospital, after another crisis which had lasted one week. Examination of the cerebrospinal fluid on February 17 showed: cells, 1 per c.mm.; protein, 30 mg. per 100 ml.; globulin, no increase; Wassermann reaction, 0.2 ml. negative; 0.5 ml. negative; 1 ml. negative; gold sol, 0000000000. At this time a test meal demonstrated histamine-fast achlorhydria, and a positive benzidine reaction was obtained with each specimen withdrawn. Radiography after a barium meal revealed a filling defect on the lesser curvature of the stomach, the appearance being more suggestive of carcinoma than of a simple lesion; gastroscopy confirmed the presence of an outgrowth on the lesser curvature (Dr. D. M. F. Batty).

Accordingly a second laparotomy was performed on March 24 (Mr. J. S. Jeffrey), and a diffuse area of thickening was found in the stomach wall on the lesser curvature with no enlargement of the associated glands. The distal two-thirds of the stomach was resected and subsequent histological examination showed the presence of a well-differentiated adenocarcinoma, with no evidence of spread. During convalescence the patient experienced further smouldering episodes of epigastric pain and vomiting.

He returned to his previous occupation and remained well until the first week of August, when continuous acute upper abdominal pain returned. On August 11 he re-entered hospital, and a further barium-meal examination showed a possible stenosis of the stoma. It was feared that there had been an extension of the neoplastic process, and a third laparotomy was performed (Professor Mercer), but no abnormality was found.

During the subsequent period of convalescence the crises continued to occur and were treated with morphine or pethidine hypodermically; neither drug gave complete relief from pain. Examination of the cerebrospinal fluid on December 27 showed: cells, 2 per c.mm.; protein, 50 mg. per 100 ml.; Wassermann reaction, negative; gold sol, 0000000000.

Finally, on January 8, 1951, the patient was admitted to the department of surgical neurology, where after a preliminary period of observation a right antero-lateral chordotomy was done at C. 3–4 level (Mr. F. J. Gillingham). This resulted in loss of pain and temperature sensation below the level of C. 8 on the left side, light touch remaining unimpaired. Five weeks later he left hospital and, after a short convalescence, resumed his former employment as a deep-sea fisherman. On March 27 the blood Wassermann reaction and Kahn test were negative. Nine months later he stated that he had had no further symptoms and had "never felt better."

Summary

A case of tabetic gastric crises is described which exhibited the following noteworthy features: (1) The occurrence of Argyll Robertson pupils as the only clinical sign of neurosyphilis in a patient with severe gastric crises. (2) A tendency for the crises to become more frequent and incapacitating, although both blood and spinal fluid became ultimately normal during adequate antisyphilitic treatment. (3) Suspicions of organic intra-abdominal disease strong enough to lead to laparotomy on three occasions and the discovery of a gastric carcinoma in a very early stage at the second operation. (4) Cessation of crises following unilateral chordotomy.

I wish to thank Dr. R. C. L. Batchelor for permission to publish this case.

REFERENCES

Moore, J. E. (1941). *The Modern Treatment of Syphilis*, 2nd ed., p. 436. Thomas, Springfield, Illinois.

—— (1947). *Penicillin in Syphilis*, p. 261. Blackwell Scientific Publ., Oxford.

Stokes, J. H. (1944). *Modern Clinical Syphilology*, 3rd ed., p. 1065. Saunders, Philadelphia.

TOXIC EFFECTS OF PHENYLBUTAZONE

BY

J. R. NASSIM, B.M., F.R.C.P.

Physician, St. George's and the Royal National Orthopaedic Hospitals, London

AND

THOMAS PILKINGTON, M.D., M.R.C.P.

Medical First Assistant, St. George's Hospital, London

Whilst the aetiology of rheumatoid arthritis remains an unsolved problem new therapeutic measures will constantly be tested for their power to alleviate its symptoms and in the hope of throwing some light on its causation. Phenylbutazone ("butazolidin") has lately been advocated as a drug which is likely to be a potent weapon in the treatment of rheumatic conditions (Currie, 1952).

Since the release of the drug for general use an increase in toxic reactions, occurring in from one-fifth to one-third of patients, has been reported (Loxton *et al.*, 1952; Kuzell *et al.*, 1952; Rhys Davies *et al.*, 1952; Cudkowicz and Jacobs, 1953). A warning of the dangers of its uncontrolled use was given by Hart and Johnson (1952). The principal untoward reactions are rashes, anorexia, nausea, abdominal pain, looseness of the stools, and reactivation of peptic ulcers with bleeding. As phenylbutazone is closely allied to amidopyrine chemically, it is not surprising that agranulocytosis, fatal in two instances, has been reported in several patients (*British Medical Journal*, 1952; Bershof and Oxman, 1953; Etess and Jacobson, 1953; Stifel and Burnheimer, 1953). Oedema due to sodium retention is a common but avoidable side-effect (Green and Williams, 1953).

Present Investigation

This paper is a record of our experiences with phenylbutazone during the past six months. The drug can be given either by mouth or by intramuscular injection, but as the majority of patients treated were out-patients the former route was usually employed. All patients were warned of possible side-effects and were asked to restrict their salt intake; those who gave a definite history of peptic ulceration or cardiovascular or renal disease were not treated with the drug. Three patients were suffering from diabetes, which was not affected by phenylbutazone.

The series consisted in 109 patients (79 women and 30 men), their ages ranging from 12 to 73 years (average age 49 years). Of these patients 86 suffered from rheumatoid arthritis, 19 from osteoarthritis, and 3 from gout. One patient had a ligamentous strain of the knee. In 18 patients phenylbutazone was combined with cortisone, but in only 4 was the effect good enough to allow the hormone to be completely withheld.

The drug was given to 102 patients by mouth in tablets containing 0.2 g. in daily doses ranging from 0.2 to 1.2 g. (average dose 0.6 g.). Seven received intramuscular injections of 1 g. on four alternate days, followed by weekly injections. All patients were seen first at weekly, then fortnightly, and, later, monthly intervals. A check was kept on the white blood count and the sedimentation rate.

Results

Symptomatically 59 patients were greatly improved by phenylbutazone, but in none was there any associated fall in the sedimentation rate. In 15 improvement was only slight, in 25 the drug had no beneficial effect, and in 10 toxic reactions occurred before any therapeutic effect could be noted.

Toxic side-reactions severe enough to necessitate stopping the drug occurred in 46 patients. The following reactions, usually in various combinations, were noted: (1) Twenty-one patients noticed severe anorexia and upper abdominal pain, one of these also having looseness of the bowels. (2) Seventeen complained of dryness of the mouth and throat, and were found to have redness of the anterior faucial pillars and uvula. Two of these had actual ulceration, which in one caused a submaxillary abscess requiring surgical drainage. Blood counts remained normal in this group. (3) Sixteen developed punctate erythematous rashes. (4) Two had enlargement of the glands in the posterior triangles of the neck. (5) One patient suffered from severe vertigo. (6) One developed granulopenia, recovering after the drug was withheld; white blood count 1,700, neutrophils 39%. The white count before treatment was 12,000, neutrophils 79%. Several patients showed a transient eosinophilia. (7) Three patients had exacerbations of the rheumatoid lesions of their hands.

Sodium retention was thought to be responsible for the slight gain in weight noticed in most patients, but only two developed pronounced oedema. This disappeared in one after salt restriction, which had not been carried out as requested, but persisted despite these measures in the other.

Response to Phenylbutazone Compared with Toxic Reactions

Response	No.	No. of Toxic Reactions Noted
In All Patients Treated		
Complete symptomatic relief	31 } 59	15 } 26
Marked " "	28 }	11 }
Analgesic effect, similar to aspirin	15	7
No symptomatic relief	25	3
Drug not given long enough to observe therapeutic effect	10	10
Total	109	46
In Patients Suffering from Rheumatoid Arthritis		
Complete symptomatic relief	28 } 48	14 } 22
Marked " "	20 }	8 }
Analgesic effect, similar to aspirin	11	6
No symptomatic relief	20	2
Drug not given long enough to observe therapeutic effect	7	7
Total	86	37

These reactions occurred on the average after three weeks, and in only two patients after three months. They were not related to dose or mode of administration, and promptly disappeared when the drug was omitted. A change from oral to parenteral therapy seemed to make no difference.

The most distressing aspect of phenylbutazone is apparent when its antirheumatic effects are compared with its toxic effects: the drug had to be withheld from nearly half the patients gaining most benefit from it, and those suffering from rheumatoid arthritis relapsed after its withdrawal (see Table).

Conclusion

We have found, as have most other authors, that phenylbutazone is a most effective weapon in combating the symptoms of rheumatoid arthritis and acute gout. However, it induced in nearly half of our patients toxic reactions severe enough to make further therapy dangerous. Nevertheless its trial in chronic disabling conditions seems justifiable, since there are a large number of patients who derive benefit without toxic manifestations; scarce supplies of A.C.T.H. and cortisone may thus be conserved. It has recently been suggested that if used in doses not exceeding 0.4 g. every 1 to 10 days only transient rashes are likely to be encountered (Lawrence, 1953). This mode of administration certainly deserves further trial.

Summary

Phenylbutazone was given to 109 patients suffering from various rheumatic conditions. Forty-six patients suffered from toxic reactions. These occurred in nearly half of those deriving great benefit. The diabetic condition of three patients receiving the drug was not affected by it. Its use is justifiable where careful and continuous control is possible.

References

Bershof, E., and Oxman, A. C. (1953). *J. Amer. med. Ass.*, **151**, 557.
British Medical Journal, 1952, **2**, 1427.
Cudkowicz, L., and Jacobs, J. H. (1953). *Lancet*, **1**, 223.
Currie, J. P. (1952). Ibid., **2**, 15.
Davies, R. H., Barter, R. W., Gee, A., and Hirson, C. (1952). *British Medical Journal*, **2**, 1392.
Etess, A. D., and Jacobson, A. S. (1953). *J. Amer. med. Ass.*, **151**, 639.
Green, J., and Williams, P. O. (1953). *Lancet*, **1**, 575.
Hart, F. D., and Johnson, A. M. (1952). Ibid., **2**, 197.
Kuzell, W. C., Schaffarzick, R. W., Brown, B., and Mankle, E. A. (1952). *J. Amer. med. Ass.*, **149**, 729.
Lawrence, J. S. (1953). *British Medical Journal*, **1**, 276.
Loxton, E. G., Le Vay, D., and Wilson, P. (1952). *Lancet*, **2**, 682.
Stifel, J. L., and Burnheimer, J. C. (1953). *J. Amer. med. Ass.*, **151**, 555.

TOXIC EFFECTS OF PHENYLBUTAZONE

WITH SPECIAL REFERENCE TO DISORDERS OF THE BLOOD

BY

J. C. LEONARD, M.D.

(*From the Ipswich Borough General Hospital*)

During the past nine months many reports on the use of phenylbutazone (" butazolidin ") in rheumatoid arthritis and allied diseases have appeared in the literature. The incidence and severity of toxic reactions have varied widely, as may be seen from the Table printed overleaf. Thus Peebles-Brown and Currie (1952) described only five toxic effects out of 280 patients (an incidence of 1.8%). On the other hand, Cudkowicz and Jacobs (1953) reported an incidence of 52%, and Stephens *et al.* (1952) one of 44%. Details of the 356 reactions in 1,526 patients have now been reported—an average incidence of 22%. This figure agrees closely with the estimate of Loxton *et al.* (1952).

The most frequent complications are by now well recognized. Oedema occurred in 84 patients; it is due to retention of sodium and water, and has often precipitated cardiac failure. Various gastro-intestinal symptoms (nausea, vomiting, diarrhoea, " gastritis ") are also common, but rarely have serious consequences; more grave, however, is the reactivation of peptic ulcer (17 patients) and haematemesis and melaena (13 patients). The latter was the cause of death in one case reported in the *British Medical Journal* (1952). Jaundice has been recorded in six patients. Skin rashes are common (51 patients) and seem to be protean in variety. Miscellaneous effects include vertigo, euphoria, conjunctivitis, haematuria, albuminuria, " haemorrhagic myelitis," and stomatitis.

The effects on the blood seem to include depression of any or all of the cellular elements. Thus Stephens *et al.* (1952) reported a fall in haemoglobin of 1 g. per 100 ml. or more in 18 out of 188 patients, and a fall in the platelet count below 100,000 per c.mm. was even more common (31 patients). Eleven cases of frank agranulocytosis, with one death, have so far been recorded, and there have been several other cases of granulocytopenia.

The case histories of two patients are described below; the first developed aplastic anaemia, and the second agranulocytosis, during treatment with phenylbutazone. The former seems to be the first case of this complication described in the literature, if one excludes the case of Kuzell *et al.* (1952a); this patient was already suffering

from monocytic leukaemia, and was receiving *x*-ray therapy simultaneously with phenylbutazone. One month previously he had also been treated with amidopyrine. The cause of the anaemia is therefore doubtful.

Case 1

A 64-year-old woman was admitted on September 16, 1952. Four years previously myxoedema had been diagnosed, and since then she had received 2 gr. (0.13 g.) of thyroid extract daily. In April, 1952, she complained of stiffness and pain in the knees, hips, shoulders, and neck. She was otherwise well. On examination there was swelling and limitation of movement in the affected joints, and rheumatoid arthritis was diagnosed. There was no clinical evidence of myxoedema, and her pulse rate varied between 80 and 100. Her erythrocyte sedimentation rate (Wintrobe) was 40 mm., and a blood count showed: haemoglobin, 77% (11.1 g.); white cells, 6,800 (polymorphs 75%, lymphocytes 25%). The serum cholesterol was 191 mg. per 100 ml. From October 11 to 26 she was treated with A.C.T.H., a total of 0.82 g. being given. This produced a satisfactory remission, but she relapsed immediately the drug was stopped. The haemoglobin on October 13 was 65% (9.3 g.). On October 28 she began a course of gold, receiving 0.44 g. in all. This produced a rash, and in view of the absence of symptomatic improvement the drug was discontinued on November 28. The white-cell count on November 25 was 5,400 (polymorphs 69%, lymphocytes 31%) and the E.S.R. 24 mm. She was discharged on December 2. When seen in the out-patient department on January 6, 1953, there was no rash, and, apart from general stiffness, she was well.

From January 14 she received 0.6 g. of phenylbutazone daily for 14 days. During this time there was slight bleeding from the nose and mouth, and on January 21 her doctor noted a purpuric rash on the legs. This was not thought to be of serious import and phenylbutazone treatment was continued, with satisfactory relief of pain. On January 28 she was found to be severely anaemic and breathless, and was readmitted as an emergency.

On examination there was evidence of bleeding from the nose, and her sputum contained small amounts of blood. There was slight congestion of the neck veins, but no oedema. Her pulse rate was 120. Her heart sounds were normal and blood pressure 124/60. Her respirations were rapid and laboured; there were coarse rales and rhonchi throughout the chest. Multiple petechial haemorrhages were present all over the body. Examination of the blood showed: haemoglobin, 26% (3.8 g.); white cells 3,200 (polymorphs 75%, lymphocytes 25%). A diagnosis of anaemic heart failure was made, and she was treated with a slow intravenous transfusion of packed cells. She died suddenly 24 hours after admission.

At necropsy a diffuse subdural haemorrhage was present, completely lining the dura in a thin layer. The lungs were deeply congested and firm. On the cut surfaces there were many nodular areas, due to diffuse haemorrhage. Multiple haemorrhages were present beneath the surface of the pericardium. The heart muscle was pale and flabby. The stomach showed small haemorrhages beneath the lining, and contained a small amount of blood. The liver was extremely pale and rather flabby. The spleen was slightly enlarged. The thyroid showed replacement by homogeneous white fibrous tissue. The bone marrow of the sternum showed considerable fatty change. At the upper end of the femur the bone marrow was partly fatty; elsewhere in the femur and in the tibia it was completely fatty.

Microscopical examination of the bone marrow from the upper end of the femur showed that cells of the erythropoietic and megakaryocyte series were entirely absent. There was also complete cessation of leucopoiesis apart from the presence of occasional myelocytes. Most of the sinuses were filled with plasma cells; these were mainly of large size, with fine cytoplasmic vacuolation. Binucleate forms were frequent. Occasional larger cell aggregates were seen; these consisted of plasma cells, with lymphocytes and reticulum cells.

Case 2

A man aged 53 had had moderately severe rheumatoid arthritis for 35 years. He was treated with phenylbutazone for six weeks; during the first week he received 1.6 g. daily, and thereafter 0.8 g. daily. After five weeks his white-cell count was 8,700 (polymorphs 55%, lymphocytes 44%, basophils 1%). One week later he complained of a sore throat and was admitted to hospital.

On examination he was not severely ill. His temperature was 101° F. (38.3° C.). His throat was reddened, but there were no palpable cervical lymph nodes. The typical deformities of rheumatoid arthritis were present in the hands and feet. Subcutaneous nodules were present over both olecranon processes and along the posterior borders of the ulnae. The left supratrochlear gland was palpable. Examination of the blood showed: haemoglobin, 100% (14.5 g.); white cells, 1,600 (polymorphs 34%, lymphocytes 47%, mononuclears 5%, eosinophils 7%, myeloblasts and myelocytes 5%, plasma cells 2%); platelets "plentiful." Phenylbutazone was stopped and he was treated with penicillin; he made an uneventful recovery. He had received no other drugs known to affect the bone marrow.

Discussion

Case 1 immediately poses the problem of whether gold or phenylbutazone was responsible for the aplastic anaemia. In 1948 Fitzpatrick and Schwartz reported that 20 cases of aplastic anaemia due to gold had been described in the literature; one of the cases did not develop the anaemia until five months after gold treatment was stopped (Aubert, 1946). When one recalls how widespread has been the employment of chrysotherapy, it is evident that the condition must be exceedingly rare. It is possible that gold

Details of Toxic Effects of Phenylbutazone

	Cudkowicz and Jacobs (1953)	Davies *et. al.* (1952)	Granirer (1952)	Hart and Johnson (1952)	Kuzell *et al.* (1952a)	Kuzell *et al.* (1952b)	Loxton *et al.* (1952)	Peebles-Brown and Currie (1952)	Shulman (1952)	Solomon (1953)	Stephens *et al.* (1952)	Others	Total
Oedema	8	8	6	3	17	24	3	2	2		9	2	84
Nausea, vomiting, diarrhoea	6	25		2	20	31					2		86
Haematemesis and melaena	2		1	3		2					2	3	13
Activation of peptic ulcer	2		1		4	3					7		17
Jaundice										2		4	6
Skin rashes	5	3	4	6	6	12	5	1			9		51
Anaemia			3		2	2					18		25
Agranulocytosis						2	1					8	11
Purpura and thrombocytopenia		1				2					31		34
Miscellaneous	3	3	5		3	6	1	2	1		5		29
Total No. of toxic effects	26	40	20	14	52	84	10	5	3	2	83	17	356
Total No. of patients treated	50	100	20	60	140	278	150	280	237	6	188	17	1,526

Observers included under "Others" column: Bourne (1953), Crowther and Elgood (1952), Hinz *et al.* (1953), Kuzell and Schaffarzick (1952), and Ross and Baldwin (1953).

was the cause of the bone-marrow aplasia in the patient under discussion. On the other hand, the patient was perfectly well (apart from arthritis) until treatment with phenylbutazone was begun; within one week she had developed epistaxis and a purpuric rash; and within two weeks a fulminating aplastic anaemia had led to death. It seems, on the whole, more reasonable to incriminate phenylbutazone, though it might be that in some way the patient had become sensitized to phenylbutazone by the previous course of gold.

Two further possibilities should be mentioned: that hypothyroidism or rheumatoid arthritis may have influenced the structure of the bone marrow in this patient. In hypothyroidism, hypoplasia of the bone marrow occurs, but the anaemia is not usually severe. As this patient had been adequately treated with thyroid extract for four years there is no reason to suppose that her myxoedema would affect the bone marrow. As regards rheumatoid arthritis, Leitner (1949) states that "in all our cases of rheumatoid arthritis we have observed plasma-cell proliferation" in the bone marrow. He cites Mester (1938), who "collected 75 cases and found an increase of plasma and reticulum cells in acute and chronic rheumatoid arthritis." Some relative proliferation of plasma cells is sometimes seen in idiopathic aplastic anaemia, but not to the same extent as in this patient. Infiltration of the bone marrow with plasma cells is, of course, a feature of multiple myelomatosis, of which there was no clinical or pathological evidence here. The relationship, if any, between plasma-cell proliferation and phenylbutazone remains to be determined.

Are the toxic effects of phenylbutazone due mainly to overdosage or to idiosyncrasy? With this question in mind, an attempt has been made to correlate the frequency of toxic reactions with the dosage of the drug administered. It seems, however, that no such broad correlation can be established, and this may indicate that idiosyncrasy to the drug is the predominant factor. Thus, on a dosage of 1 g. daily, Cudkowicz and Jacobs (1953) reported toxic effects in 26 out of 50 patients, whereas Currie (1952) reported no toxic effects in 81 patients. Loxton *et al.* gave doses varying from 0.4 to 0.8 g. daily, and reported toxic effects at each level. Of the patients with agranulocytosis, three had never received more than 0.8 g. daily, whereas two had received 1.2 g. daily. Of the present cases, Case 1 received 0.6 g. daily, a dosage normally regarded as safe, and Case 2 received 1.6 g. daily for the first week and 0.8 g. thereafter. It thus appears from these cases that the administration of small doses of phenylbutazone does not eliminate the possibility of developing serious blood dyscrasias. The possible dangers of phenylbutazone therapy are increased by its effectiveness, which encourages its employment in general practice. It would seem that its use should be closely controlled by frequent blood counts, and that it should be confined at present to patients in hospital.

Summary

Details of 356 toxic effects occurring in 1,526 patients treated with phenylbutazone have been collected from the literature (an average incidence of 22%).

A fatal case of aplastic anaemia is reported. Though the patient had also been treated with gold, it is contended that phenylbutazone was probably responsible for the anaemia.

A case of agranulocytosis due to phenylbutazone is also described.

The incidence of toxic effects does not seem to be related to the dosage of phenylbutazone, as reactions commonly develop in patients treated with small doses. It is suggested that the use of the drug should be confined at present to patients in hospital.

I wish to thank Dr. Ronald Jones for his help, criticism, and encouragement in the preparation of this paper, and for permission to publish Case 1; Dr. J. W. Paulley for permission to publish Case 2; and Dr. Trevor Shaw, who performed the necropsy.

REFERENCES

Aubert, A. (1946). *Acta med. scand.*, **123**, 377.
Bourne, W. A. (1953). *Lancet*, **1**, 1427.
British Medical Journal, 1952, **2**, 1427.
Crowther, D. L., and Elgood, F. R. M. (1952). *Lancet*, **2**, 829.
Cudkowicz, L., and Jacobs, J. H. (1953). Ibid., **1**, 223.
Currie, J. P. (1952). Ibid., **2**, 15.
Davies, H. R., *et al.* (1952). *British Medical Journal*, **2**, 1392.
Fitzpatrick, W. J., and Schwartz, S. O. (1948). *Blood*, **3**, 192.
Granirer, L. W. (1952). *J. Amer. med. Ass.*, **150**, 1332.
Hart, F. D., and Johnson, A. M. (1952). *Lancet*, **2**, 587.
Hinz, C., *et al.* (1953). *J. Amer. med. Ass.*, **151**, 38.
Kuzell, W. C., and Schaffarzick, R. W. (1952). *Bull. rheum. Dis.*, **3**, 23.
—— *et al.* (1952a). *J. Amer. med. Ass.*, **149**, 729.
—— —— (1952b). *Calif. Med.*, **77**, 319.
Leitner, S. J. (1949). *Bone Marrow Biopsy*, p. 289. Churchill, London.
Loxton, G. E., *et al.* (1952). *Lancet*, **2**, 682.
Mester, A. (1938). *Z. Rheumaforsch.*, **1**, 534.
Peebles-Brown, R. A., and Currie, J. P. (1952). *Lancet*, **2**, 682.
Ross, A., and Baldwin, D. W. (1953). *British Medical Journal*, **1**, 159.
Shulman, J. (1952). *Lancet*, **2**, 887.
Solomon, R. M. (1953). *British Medical Journal*, **1**, 159.
Stephens, C. A. L., *et al.* (1952). *J. Amer. med. Ass.*, **150**, 1084.

ETHOPROPAZINE HYDROCHLORIDE IN TREATMENT OF CEREBRAL PALSY

BY

R. G. MITCHELL, M.B., M.R.C.P.Ed., D.C.H.

(From the Westerlea School for Spastic Children, Edinburgh)

The use of drugs plays only a small part in the treatment of cerebral palsy, and so varied are the conditions grouped under this comprehensive term that a single agent is unlikely to be of value in every case. Barbiturates, anticonvulsants, and the belladonna alkaloids are the only drugs in regular use, but reports on recently developed synthetic drugs hold out hope of more effective agents in the future. Jersild (1950) reported encouraging results in congenital spastic paralysis with the synthetic spasmolytic substance caramiphen hydrochloride ("parpanit"), while improvement has been noted in cerebral palsy treated with muscle-relaxants. Some of these, such as mephenesin, may establish a place in treatment (Berger and Schwartz, 1948), while the value of others, such as neostigmine, has not been confirmed (Perlstein and Barnett, 1950).

The beneficial effect of antihistaminic and related drugs in parkinsonism (Sigwald, 1949; Palmer and Gallagher, 1950) suggests their possible value in cerebral palsy, especially in cases in which extrapyramidal signs predominate. Opinions vary on the relative merits of these agents in the treatment of parkinsonism; Garai (1951) found that improvement with benzhexol hydrochloride ("artane") was greater than with ethopropazine ("lysivane"), whereas Gillhespy (1951) considered that ethopropazine was superior to all other drugs of this series.

Effron and Schultz (1951) reported that benzhexol hydrochloride was relatively ineffective in the treatment of eight patients with cerebral palsy. In the present investigation, ethopropazine was chosen because of the favourable impression created by the treatment of a few selected out-patients with this drug.

Details of the Investigation

The trial of ethopropazine was carried out at a residential school for children with cerebral palsy. The school is equipped with physiotherapy, occupational therapy, and speech therapy departments, all of which took part in the investigation.

The 19 children at the school comprised 6 with spastic tetraplegia, 4 with spastic paraplegia, 7 athetoid, and 2 ataxic, their ages ranging from 5 to 14 years. None of them was mentally retarded and all were moderately to severely handicapped. The children were arranged in pairs of approximately the same age and type of palsy, and were then divided into two groups without further selection. The groups were therefore comparable in age distribution and in type and degree of disability; one group was given ethopropazine and the other constituted a control group.

The trial was confined to school terms, since in the holidays the children return to their homes, making supervision impossible. When the children return to school after the holidays some are usually found to have regressed slightly, so that the trial was not begun until three weeks after the beginning of term, to allow for the expected improvement. This left a period of about seven weeks for the trial, and it was decided to give the drug for four weeks in order to assess the child's performance before treatment and to ensure supervision for a week after stopping the drug, in case of possible withdrawal effects. Although four weeks is not a long period, it was thought to be long enough for any improvement to be evident.

The trial was divided into two parts, the 10 spastic children being tested in the first term and the 9 athetoid and ataxic children in the second term. This division was necessary because of the time involved in carrying out accurate tests, which imposed considerable extra demands on the staff of the school.

Dosage of Ethopropazine.—The ethopropazine was supplied in 10-mg. sugar-coated tablets, and the control tablets were identical in appearance but contained lactose. The tablets were administered in four divided doses during the day, each child in the control group receiving the same number of tablets as his equal in the trial group. In the first half of the trial the starting dose was 20 to 30 mg. daily, depending on age, and the dose was increased by 10 to 20 mg. a day at intervals of four days, until a maximum of 100 to 150 mg. daily was reached. In the second half of the trial the starting dose was 30 to 50 mg. daily, and the dose was increased by 20 to 30 mg. a day at intervals of four days, to a maximum of 200 to 250 mg. daily.

Methods of Assessment

Once a week, on the same day each week, the children's progress was assessed, using a number of tests designed to measure different activities. The time taken for each test was measured in seconds with a stop-watch, the final figure being the mean of at least three attempts. The tests used were as follows:

A tests measured ability to relax—for example, the time for which the child could maintain his lips together or could lie still without moving.

B tests measured balance—for example, the time for which the child could hold his head steady or could stand on one leg.

C tests measured active movement—for example, the speed of rising from supine to sitting or standing positions, or the time taken to flex and extend the elbow a given number of times.

D tests measured manual dexterity—for example, the time taken to transfer articles from one container to another, or to take out and replace pegs on a board.

E tests measured speed of rolling—for example, the time taken to roll a measured distance on the floor.

Every child was tested in at least three activities, and, although the tests were adapted to suit the individual child, each performed the same tests each week and did not carry them out at other times during the week.

Speech records were made before the beginning of the trial and again when the children were receiving the maximum dose. The school teachers were also asked to note any changes in ability in the class-room, and the children were under constant supervision by the resident nursing sister. The sister was the only person in the school who knew which children were receiving ethopropazine and which the control tablets.

Results

The results of the trial are presented in the accompanying table. A child's performance for each activity in which he was tested was recorded as having improved or as showing no change. An improvement was regarded as having taken place if either of two criteria was satisfied: (1) if progressive and uninterrupted improvement occurred while the child was receiving the tablets; or (2) if the mean performance during the trial period was at least 100% better than the mean performance when no tablets were being given.

Only one child, No. 3 in the table, improved in all tests. This was a girl of 13 years with severe spastic tetraplegia, and the improvement was maintained permanently after completion of the trial, so that it is difficult to attribute it to the ethopropazine. An assessment of improvement based on the total number of tests performed shows that 23.3% improvement occurred in the trial group and 22.2% improvement in the control group. When the different types of cerebral palsy are considered, no consistent improvement in one type or in one activity is found, though the numbers in each group are too small for definite conclusions to be drawn.

Results of Trial

Type of Cerebral Palsy	Case No.	Improved	No Change
Group Receiving Ethopropazine			
Spastic	1	—	C D E
	2	—	C D E
	3	C E D	—
	4	—	C D E
	5	—	C D E
Athetoid	6	—	A B D
	7	A	C D
	8	A D	B
	9	B	A D
Ataxic	10	—	B C D
Totals of 30 tests on 10 patients		7 (23·3%)	23 (76·7%)
Group Receiving Control Tablets			
Spastic	11	D E	C
	12	—	C D E
	13	—	C D E
	14	C D	E
	15	—	C D E
Athetoid	16	—	A C D
	17	D	B C
	18	D	A B
Ataxic	19	—	B C D
Totals of 27 tests on 9 patients		6 (22·2%)	21 (77·8%)

The speech records made before and during the trial were carefully compared; two of the ethopropazine group and three of the control group were regarded as having improved slightly. The school teachers noted no unusual improvement in ability in any of the children.

Toxic Effects of Ethopropazine.—In the first half of the trial no toxic effects were noted. In the second half three children, aged 8½, 8, and 7 years, became rather drowsy and listless when a daily dosage of 140, 120, and 140 mg. respectively was reached. In none of these children were the symptoms severe enough to necessitate withdrawal of the drug. Total and differential leucocyte counts were carried out before and at intervals during the administration of the tablets. In no case did a significant reduction in the number of leucocytes occur. On completion of the trial, administration of the drug was stopped abruptly. None of the children showed symptoms of withdrawal except for one boy who developed severe constipation, which might possibly have been due to withdrawal. The three children who showed toxic symptoms became normally alert within 48 hours of stopping the drug.

Summary and Conclusions

The results of a trial of ethopropazine in the treatment of cerebral palsy are recorded. Ten children with various types of cerebral palsy were given ethopropazine and a comparable group of nine children received lactose control tablets.

There was an improvement of 23.3% in the children treated with ethopropazine, but a similar improvement occurred in those who received only lactose tablets. No evidence of a special effect of ethopropazine on any type of cerebral palsy or on any specific ability was obtained. It is therefore concluded that ethopropazine is of no value in the treatment of cerebral palsy.

This trial was carried out under the auspices of the Scottish Council for the Care of Spastics. I wish to thank the staff of Westerlea School for their willing co-operation and Messrs. May and Baker Ltd. for generously supplying the lysivane.

REFERENCES

Berger, F. M., and Schwartz, R. P. (1948). *J. Amer. med. Ass.*, **137**, 772.
Effron, A. S., and Schultz, W. M. (1951). *Amer. J. med. Sci.*, **221**, 561.
Garai, O. (1951). *Lancet*, **1**, 429.
Gillhespy, R. O. (1951). *British Medical Journal*, **2**, 301.
Jersild, T. (1950). *Acta paediat., Uppsala*, **39**, 51.
Palmer, H., and Gallagher, D. J. A. (1950). *British Medical Journal*, **2**, 558.
Perlstein, M. A., and Barnett, H. E. (1950). *J. Amer. med. Ass.*, **142**, 403.
Sigwald, I. (1949). *Presse méd.*, **57**, 819.

ADRENALINE NECROSIS

BY

G. LESLIE, M.D.

Senior Registrar, Department of Dermatology, Royal Infirmary, Glasgow

AND

D. McPHEE, M.D., B.Sc.

Tissue necrosis due to adrenaline injections is a rare occurrence when it is considered how often the drug is administered.

Urbach (1936) reported a case in which multiple areas of skin necrosis followed the self-administration of adrenaline by a female patient who suffered from severe bronchial asthma. To gain relief she often gave herself as many as three injections a night. Urbach observed insistent "intention tremor" at the time of injection, which often took as long as fifteen minutes to complete. When the injection was given to the patient he was unable to get the slightest reaction in the skin. Again, when the patient herself administered an injection of normal saline there were no visible changes in the skin. In this way it was shown that the damage produced by the adrenaline injections was not due solely to mechanical irritation. Urbach concluded that the trauma caused by the "intention tremor" combined with the constriction of the blood vessels, due to the adrenaline, produced a necrosis of the superficial skin.

Necrosis of the tips of two fingers of the hand of a patient operated upon for Dupuytren's contracture was noted by Hanke (1936). The local analgesic used was a 1% procaine-adrenaline solution, the adrenaline being added in the correct dosage just before the injection. He thought that the explanation of this was that the anaesthetizing fluid had acted over a prolonged period on tissue devitalized by the gradual contraction of the palmar aponeurosis which is a feature of the disease.

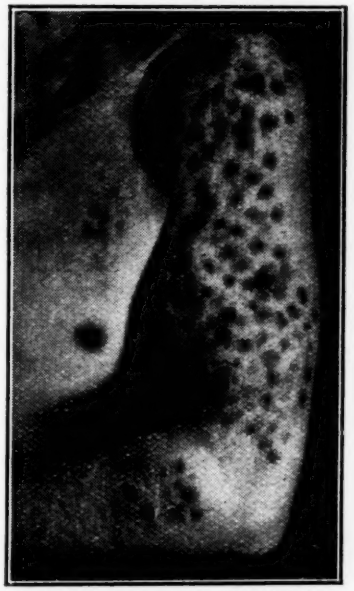
The most recent case of tissue damage due to the self-administration of adrenaline was reported by Robertson (1951). In his case the tissue reaction was that of keloid formation, which was presumably a personal skin characteristic and due to trauma with a hypodermic needle.

Delaunay *et al.* (1948) conducted a series of experiments, injecting adrenaline in various strengths (1,000 μg., 200 μg., 100 μg., 50 μg., 33 μg., 25 μg., 20 μg., and 10 μg.) under the skin of the abdomen of guinea-pigs. The stronger solutions (1,000–25 μg.) produced changes in the skin visible to the naked eye. With the weaker solutions reactions were noted microscopically. These workers think that adrenaline is not directly toxic to tissues, but that adrenaline necrosis arises rather from various vascular disturbances. They suggest that both vasomotor upsets and disturbance of the permeability of the vessels play a part by interfering with the oxygen supply to the tissues and by inhibiting the diapedesis of polymorphs.

Because of the seeming rarity of skin reactions to the repeated use of adrenaline, and because trauma has apparently played some part in the causation of the cases reported, it was thought that the following case was worth recording.

Case Report

A joiner aged 35 developed asthma at the age of 14, and, after prolonged treatment with various remedies, he obtained relief only from injections of adrenaline. About five years ago his attacks became more frequent and severe, totally incapacitating him, and he found it necessary to give himself adrenaline by injection (1 ml. of 1/1,000 three or four times daily). He became so dependent upon the adrenaline that he administered it as a routine in anticipation of an asthmatic attack. These injections continued for two and a half years without any noticeable cutaneous reaction, the dose remaining the same. He first noticed, at the site of injection, a small red swelling which was painless and did not itch. The surface of the swelling then broke down and a necrotic central patch developed. A black eschar was eventually sloughed and a shallow ulcer remained. This sequence of events took seven to ten days. The ulcer healed slowly, leaving a foveated scar, which later became livid.



Photograph showing active, healing, and healed necrotic areas.

In spite of these reactions he continued to give himself the injections, in the same dose, for a further period of two and a half years, at which time he was seen by one of us (D. McP.).

On examination his appearance was startling. His buttocks, thighs, arms, and shoulders were covered by a multitude of active, healing, and healed necrotic areas of almost uniform size and shape. He was beginning to run short of accessible parts on the limbs and was encroaching on the chest (see Fig.). Until the onset of the skin reactions the right and left arms had been used alternately for the injec-

tions. His general condition was good and nothing abnormal was detected in any of the vital systems. During a series of readings the blood pressure remained in the region of 127/80.

Comment

Trauma does not seem to have played any part in the causation of the skin reactions in this case. The injections were administered for two and a half years without any visible skin change, and while, so far as the arms are concerned, trauma from repeated injections could have been a causative factor, this cannot be said of the new areas of skin used after the onset of the cutaneous reactions, as necrotic lesions developed on these even after the first injection into them, and continued to develop after each fresh injection until all accessible areas on the limbs had been exhausted and encroachment on to the chest wall had begun. This would suggest that the patient had developed a specific sensitivity to adrenaline, localized to the area of injection and affecting the blood vessels. This is in accord with Delaunay *et al.*, who considered, from their experimental work with guinea-pigs, that the skin reactions were of an allergic nature.

Summary

A case of necrosis of the skin after prolonged self-administration of adrenaline by injection, in an asthmatic patient, is described.

Trauma, which was a possible causative factor in some of the cases reported, did not seem to play a part in this case.

It is suggested that an allergy to adrenaline developed after repeated injections over a long period and that this is in accord with the experimental findings of Delaunay *et al.*

REFERENCES

Delaunay, A., Delaunay, M., and Lebrun, J. (1948). *C.R. Acad. Sci., Paris*, 227, 314.
Hanke, H. (1936). *Chirurg.*, 8, 684.
Robertson, C. K. (1951). *Edinb. med. J.*, 58, 555.
Urbach, E. (1936). *Med. Klin.*, 32, 769.

Medical Memorandum

Torsion of a Mesenteric Lymphatic Cyst

Intra-abdominal lymphangiomata or lymphatic cysts seem to occur most commonly in the great omentum, and it is extremely rare for them to develop in the mesentery (Macnab and Menzies, 1950). As they are usually discovered accidentally during an exploratory laparotomy, the following case is of interest.

CASE REPORT

Abdominal pain began at 3.30 p.m. on October 2, 1951, in a boy aged 3½ years. After a normal bowel action the pain disappeared, but it came back at 8 o'clock the same evening. The child cried throughout the night and complained of pain in the abdomen and back, and said that he could not sit up in bed. He did not vomit but his appetite was poor. He also complained of pain in the abdomen while passing urine, and, although this was clear, his mother noticed that it had a strong odour.

The child was admitted to hospital at 2 p.m. on October 3 and was obviously ill. His temperature was 100.4° F. (38° C.), pulse rate 140, and respirations 28. Abdominal examination revealed some tenderness and rigidity on the right side, mainly below the umbilicus. The tongue was coated and a little "smelly." Rectal examination revealed some tenderness on the right side of the pelvis. The heart, lungs, and nervous system showed no abnormality, and the urine was normal. The history and physical signs at this stage suggested an acute appendicitis. A few hours later the abdomen became completely rigid on both sides, more so below the umbilicus, and a laparotomy was decided upon.

Operation.—As soon as the child was under the anaesthetic a swelling in the abdomen was visible to the naked eye. This was about 3 in. (7.5 cm.) in diameter, was hard, and was freely movable in all directions. Its position was approximately central in the abdomen, and a hand could be placed beneath it above the symphysis pubis. A right paramedian incision was made and the peritoneum was opened. A small amount of serous effusion was found, together with clots of fibrinous exudate, which appeared to be mainly present on the common and external iliac vessels on the right side. The appendix appeared normal. The swelling was seen in the hypogastrium and looked tense and purplish in colour, and on its delivery through the wound it underwent a spontaneous untwisting. It appeared to be a multilocular cyst in the mesentery of the ileum, approximately 2 ft. (60 cm.) from the ileo-caecal junction. The cyst was in actual contact with the intestinal wall, enveloping the ileum on three sides in a U-shaped manner. It did not extend into the retroperitoneal tissues, nor was there any evidence of communication between it and the mucous lining of the intestine. The locules intercommunicated, and contained a blood-stained clearish fluid, together with blood clots and flakes of fibrin; the walls of the cyst except those adjacent to the ileum were excised, and the cut edges of the mesentery brought together with interrupted catgut sutures. There was no evidence of intestinal obstruction, the colour of the ileum improving after the untwisting.

A course of "distaquaine" penicillin and "cremomerazine" was given, the clips being removed on the fifth day, and the child began to take a normal diet. Recovery continued uninterrupted.

The section showed a cyst wall composed of fibro-elastic tissue and lined by a single layer of flat endothelium. The wall showed congestion, degeneration, and polymorphonuclear and round-cell infiltration. The pathologist stated that the appearance was that of a strangulated lymphatic cyst of the mesentery.

COMMENT

Considering the clinical aspects of mesenteric cysts as a whole, Aird (1950) states that usually the only sign is that of a floating abdominal tumour, which is painless unless the cysts become infected from the bowel, when they lose their mobility and adopt the features of a well-localized abdominal abscess. In this case there was no infection, and the tumour was not palpable before the anaesthetic was given. Macnab and Menzies (1950) say that these cysts do not produce a constant clinical picture. They may present as an abdominal catastrophe, as in this case. Severe pain, vomiting, and abdominal rigidity may predominate, or there may be just an ill-defined malaise. The history of each case seems to be determined by the complications which have occurred. One-third of the cases produced intestinal obstruction (Waters, 1946). The cysts may undergo torsion, as in this case, or produce an intestinal volvulus. They may rupture into the peritoneal cavity and simulate acute peritonitis, or ruptured tubal gestation in women. They may become infected and present as an acute appendicitis or diverticulitis.

Regarding their aetiology, Lord Moynihan (1897) stated that they were simple dilatations of lymphatic vessels. Illingworth and Dick (1949) favour the view that they are dilatations of lymph vascular networks present in embryonic life, like cystic hygroma in the neck.

My thanks are due to Mr. P. H. Merlin, consultant surgeon, for permission to publish this case.

N. V. ADDISON, M.B., Ch.B.,
Dewsbury General Hospital.

REFERENCES

Aird, I. (1950). *Companion to Surgical Studies*, p. 568. Livingstone, Edinburgh.
Illingworth, C. F. W., and Dick, B. M. (1949). *Textbook of Surgical Pathology*, p. 554. Churchill, London.
Macnab, I., and Menzies, T. (1950). *Brit. J. Surg.*, 37, 294.
Moynihan, B. G. A. (1897). *Ann. Surg.*, 26, 1.
Waters, E. G. (1946). *Amer. J. Obstet. Gynec.*, 52, 478. Quoted by Macnab and Menzies (1950).

Reviews

CORTISONE AND A.C.T.H.

Cortisone and A.C.T.H. in Clinical Practice. Under the general Editorship of W. S. C. Copeman, O.B.E., M.D., F.R.C.P. With foreword by Lord Horder, G.C.V.O., M.D., F.R.C.P. (Pp. 255; 35 illustrations. £1 5s.) London: Butterworth and Co. 1953.

In the four years which have passed since Hench and his colleagues of the Mayo Clinic discovered the dramatic effects of cortisone in rheumatoid arthritis, verdicts on its ultimate role in therapy have ranged from "elixir vitae" to "glorified aspirin." In this book seven distinguished British authorities, who have had special opportunities for the clinical investigation of cortisone and A.C.T.H., record their own experiences and present a sober appraisal of the writings of others. Each article bears a personal stamp and reveals how the initial unrestrained enthusiasms have been tempered by time and experience.

The rheumatic and collagen diseases are discussed by Oswald Savage and W. S. C. Copeman, diseases of the eye by Mary Savory and Arnold Sorsby, endocrine disorders and respiratory and allergic diseases by F. Dudley Hart, skin diseases by G. B. Mitchell-Heggs, and diseases of the haemopoietic system by J. W. Stewart.

The specific value of these hormones in the diagnosis and treatment of both primary and secondary adrenal insufficiency is illustrated by a wealth of clinical material, and the important part played by cortisone in the post-operative care of bilateral adrenalectomy for such conditions as hypertension and basophilism is established. All authors emphasize that, apart from substitution therapy, cortisone and A.C.T.H. are not curative; that these hormones do not replace, but where helpful are complementary to, established therapeutic measures; that the individual response is very variable; and that before these drugs are exhibited the possible therapeutic benefits must be carefully weighed against the gravity and severity of potential toxic and withdrawal symptoms.

In a few diseases—for example, disseminated lupus erythematosus and pemphigus—cortisone may be a life-saving or life-prolonging measure. In conditions of limited duration, such as iridocyclitis, it may abort or control the inflammatory process in such a way that grave risks to vision may be circumvented. In others it relieves immediate discomforts, as in some allergic states; while in yet others it preserves function and avoids crippling, as in rheumatoid arthritis. In rheumatic fever its value is still in doubt. In the vast majority of diseased states cortisone is without significant effect. In some indeed it aggravates the pathological process—for example, by disseminating tuberculosis or by the perforation of a peptic or colitic ulcer.

There is a brief but adequate account of the physiology and pharmacology of cortisone and A.C.T.H. and of the gaps in our understanding of many fundamental aspects of their mode of action. But this is essentially a clinical manual and the emphasis throughout is on practical rather than theoretical problems. The bibliography is extensive, well chosen, and up to date, and careful editing has avoided undue overlap. In short, this book provides an accurate, informed, concise, and lucid survey of current opinions on the value and limitations of cortisone and A.C.T.H. therapy.

There is, however, a major lapse which, while not detracting from the technical merits of the book, grieves the literary purist. The quotation attributed to Alexander Pope on the verso of the preface reads:

> Be not the first to cast the old aside,
> Nor yet the first by whom the new is tried.

But Pope wrote in his *Essay on Criticism*:

> Be not the first by whom the new are tried,
> Nor yet the last to lay the old aside.

And most of us will prefer the original.

HENRY COHEN.

TEXTBOOK OF PAEDIATRICS

Pédiatrie. Volumes I and II. By Robert Debré and Marcel Lelong. (Pp. 2,260; 388 figures. 14,500 francs.) Paris: Les Éditions Médicales Flammarion. 1952.

This massive two-volume work is the latest of the series of publications under the general editorship of Dr. Vallery-Radot which are arranged on the loose-leaf system for annual revision. The two editors, Professors Debré and Lelong, are both paediatricians of international repute, and they have the assistance of 38 contributors. Unfortunately, the individual contributors responsible for the different sections remain unknown, for the editors have modified each chapter so as to provide uniformity of style and teaching to fit in with their plans. The work is up to date and well presented. The paper and printing are excellent, and the books make easy reading. The illustrations, photographic, radiological, and tabular, are magnificent, being well chosen and perfectly reproduced. Each volume has a table of contents, but the index is in Volume II only. The attachment of the pages to the covers is inadequate for such heavy books, and it is to be hoped that the binding system may be improved at the next printing.

As might be expected, eponyms abound. More than 160 eponymous diseases are listed in the index—most of them French. Acute rheumatism, for example, is referred to as Bouillard's disease, rheumatic nodules are Meynet's nodules, erythema marginatum is Besnier's erythema, and chorea becomes "la danse de Saint-Guy." The sections on tuberculosis and the cardiovascular system in Volume I and on the blood and haematopoietic organs in Volume II are outstanding. Treatment advised is not always in accord with generally accepted principles. Rectal administration of sodium salicylate in milk is unlikely to be widely used in the treatment of rheumatism, nor is a fixation abscess the treatment of choice in acute encephalitis. The strict dietetic restriction in acute nephritis, in vogue in 1826, is still recommended, and venesection is advised for convulsions in this disease. The modern conception of coeliac disease is not discussed, and no reference is made to the work of Frazer, Sheldon, and Dicke in this field. Von Jaksch's anaemia and Hanot's cirrhosis still find a place, though they have disappeared from most other modern paediatric textbooks. It is a pity that the exanthemata are excluded, for they are essentially paediatric, but they have already been covered in another volume in the same series.

For the postgraduate student of paediatrics and for the general practitioner this work is a distinct asset, and if the annual supplements for insertion maintain the standard set in these initial volumes their value will be enhanced still further.

WILFRID GAISFORD.

MICROSCOPY

Handbook of Basic Microtechnique. By Peter Gray, Ph.D., D.I.C. (Pp. 141; 57 figures. 12s. 6d.) London: Constable and Co. 1953.

Lecture Notes on the Use of the Microscope. By R. Barer, M.C., M.A., B.Sc., M.B., B.S. (Pp. 76; 8 figures. 6s.) Oxford: Blackwell Scientific Publications. 1953.

Dr. Gray's book sets out the fundamentals of histological technique for university students and laboratory technicians, especially in zoology and botany. Part I is a general account of the materials and processes of slide-making. Its various chapters are on apparatus, fixatives, stains, dehydrating and clearing agents, mounting media, wholemounts, smears, sections, and the cleaning, labelling, and storing of slides. Part II—the last third of the book—consists of fifteen specific examples of slide-making, which collectively form a complete introductory course in plant and animal microtechnique. The author's policy was to select a few well-tried methods and reagents from the many available and to describe them in detail; alternative methods are to be given in the author's larger reference work on *Microtechnique.*

The instructions for section-cutting would interest technicians in anatomy, pathology, and bacteriology, but the material, methods, and reagents are those of the zoologist and botanist. The author is obviously a stylist as well as a scholar, for the book is most elegantly written.

Dr. Barer's book, despite its modest title, is a miniature treatise on the microscope—its structure, theory, use, and maintenance. A description of the microscope is followed by an illustrated account of the formation of the image, and careful explanations of such concepts as numerical aperture, resolving power, visibility, and contrast. Objectives, condensers, and eye-pieces are next considered, and there is an interesting account of various ways of getting a desired magnification. The second half of the book deals with the use of the microscope, methods of illumination, the care and cleaning of the microscope, and hints on a variety of practical problems. The book ends with suggestions for further reading, and appendices on experiments with the microscope and on special microscope lamps.

The book is thus wider in scope than the excellent but more strictly practical pamphlets issued by microscope makers, and contains all that the ordinary microscopist need know. The book would interest not only its intended audience—university students and senior schoolchildren—but also research workers, apprentice designers, and technicians responsible for the routine care or professional servicing of microscopes.

RAYMOND WHITEHEAD.

MALTHUS READ AGAIN

The Malthusian Population Theory. By G. F. McCleary. (Pp. 191. 15s.) London: Faber and Faber. 1953.

To the average layman and to many doctors the word "Malthusian" brings to mind lectures on "family limitation" and price-lists in plain envelopes. It is many years since a manufacturer of "specialities" perpetuated a common error by attaching the name to one of his products. In fact, in 1798 when the Rev. Thomas Robert Malthus published his *Essay on the Principle of Population* contraception was ineffective in practice and the prerogative almost solely of loose women and French aristocrats. It formed no part of his thesis and he condemned it as unnatural and vicious, a view he held to the end of his days. Among more widely read people, including reputable specialists in economics, he is equally misunderstood and misquoted as a gloomy prophet who saw in the amelioration of social conditions after the French Revolution a vision of an unchecked and idle population outgrowing its food supply. In fact he never set up as a prophet at all but was one of the first men to apply the objective methods of science to the description of existing trends in human communities.

Dr. McCleary, with his pioneer experience of problems of social welfare, and himself a demographer, sets out to remind us of what Malthus really said and of the historical and philosophical background of his theories. To this he adds an appraisal of their application at the present time notable for its clarity and humour and the absence of either medical or sociological jargon.

When he went down from Cambridge Malthus said of himself, "I had not acquired that command over my understanding which would enable me to believe what I wished without evidence," and he proceeded without rancour to take to pieces the theoretical Utopias of Condorcet and Godwin which were being hailed in England at the time and regarded as just round the corner. His originality is perhaps indicated by the fact that Darwin wrote that he was first moved to think of natural selection after reading the *Essay*. Those of us who have subscribed to some of the many misapprehensions about Malthus's theories perhaps owe it to him to reorient ourselves with the aid of this most readable and timely book.

ALEXANDER KENNEDY.

CHILD CARE

Child Care and Management: From Pre-Natal Days to Adolescence. By Patricia Edge. (Pp. 497. £1 10s.) London: Faber and Faber. 1953.

This is quite one of the best books I have read on the care of children and the help that can be given to them in preparation for adult life. It is well written in an attractive, sincere style, and the author gives sound advice on most of the questions that parents may find some difficulty in answering. The first section is on the health and hygiene of the expectant mother, and gives useful information about preparing for the baby's arrival. Subsequent sections deal with the first two years of life, the pre-school years, and then school life and adolescence. The author covers diet, hygiene, physical and mental health, and all the essential aspects of child health; in addition there are sensible discussions on such topics as homework and examinations, pocket money, hobbies, and punishments and rewards. The section on adolescence is full of wisdom and is presented in just the right form, without any unnecessary emotional colouring.

Later in the book there are sections on emotional development and character training, recreation, sickness in the home, and on choosing a career. These headings will give some idea of the breadth of the book, and the information is of the detailed kind that gives just the practical help that parents so often need. For instance, there are the addresses of appropriate organizations that may be approached in regard to the different types of career, with the approximate cost of training and so forth.

In the next edition I would like to see more specific advice about the type of cod-liver oil (p. 71) that should be given to infants, because there is a real danger of giving insufficient vitamin D; and Dr. Gesell's name is incorrectly spelt on pages 117 and 118.

This book is well worthy of recommendation.

NORMAN B. CAPON.

The second edition has now appeared of *Problems of Fertility in General Practice* by Mr. John Stallworthy, Mr. Kenneth Walker, Dr. Joan Malleson, and Dr. Margaret Jackson (Cassell, 18s. 6d.). The first part is on the investigation and treatment of sterility, the second on clinical contraception, and the third on genetical problems in general practice. In *To Define True Madness* Dr. Henry Yellowlees discusses many psychiatric problems in a form intended to appeal to the educated layman. His observations on medico-legal psychiatry would be of interest to medical as well as lay readers. The book is published by Sidgwick and Jackson for 12s. 6d. The authors of *Food Sense* describe for housewives and others the principles of sound diet, discussing in straightforward language such topics as cleanliness in preparing food, special diet in illness, and the constituents of food. Written by Dr. S. S. B. Gilder, Mr. G. M. Chapel, and Miss Louise Davies, the book is published by Ward Lock and Co. for 15s.

New editions of two well-known dictionaries have recently appeared—namely, *Black's Medical Dictionary* in its 21st edition, and *A Dictionary of Scientific Terms* in its 5th edition. New material has been added to "Black's" to bring it up to date, while pruning here and there has kept it within reasonable bounds. The dictionary had been completely revised in its previous edition, which appeared two years ago. It is published by Adam and Charles Black for 30s. The *Dictionary of Scientific Terms*, revised by Dr. J. H. Kenneth, Ph.D., covers the biological sciences and is complementary to a purely medical dictionary such as "Black's." It is published by Oliver and Boyd for 32s.

That excellent annual publication the *Commonwealth Universities Yearbook* has now appeared in its 30th edition. It gives detailed information about staff, organization, and arrangements for study and leisure in all universities in the British Commonwealth. It is published for the Association of Universities of the British Commonwealth by G. Bell and Sons, Ltd., for £3 3s. *Alumni Cantabrigienses*, Part II, Volume V, compiled by J. A. Venn, gives biographical details of all known students, graduates, and holders of office at the University of Cambridge from 1752 to 1900. The alphabetical list of names treated is Pace–Spyers. It is published by the Cambridge University Press for £10 10s.

BRITISH MEDICAL JOURNAL
LONDON
SATURDAY JUNE 13 1953

PROGNOSIS AND TREATMENT OF HYPERTENSION

Essential hypertension is a progressive disease, and its variable rate of progression makes the prognosis in any individual case a difficult problem. In cases of severe hypertension with a diastolic pressure of over 130 mm. Hg the blood-pressure level itself will indicate a bad prognosis, but in the much commoner less severe cases the degree and rate of progression of the secondary cardiovascular, retinal, and renal changes are more helpful in deciding the prognosis than the level of blood pressure, to which too much attention is perhaps apt to be paid. In those cases with no evidence of myocardial damage, clinical or electrocardiographic, and only minimal retinal changes, the disease follows a benign course even if symptoms such as severe headache are present, and most of these patients will be alive at 65.[1] A faster deterioration is indicated by advanced retinal changes, cardiac enlargement, an electrocardiogram showing left ventricular hypertrophy or strain, or signs of previous cerebral accidents, and Hammarström and Bechgaard[2] found that only 38% of their male patients would survive for five years and only 13% for ten years; the corresponding figures for women were 70% and 45%. The presence of papilloedema and retinal exudates indicates a bad prognosis, fewer than one-fifth of patients of both sexes being alive after five years.

Leishman[3] concluded that the stage which the hypertensive disease had reached could be best judged by the presence or absence of four clinical features—advanced retinal changes, albuminuria in excess of a trace, cardiac enlargement, and abnormality of the electrocardiogram. Malignant hypertension, whether the hypertension is primarily "essential" or renal in origin, is characterized clinically by papilloedema with a high diastolic pressure and pathologically by the presence of acute arteriolar necroses. Pickering[4] has suggested that these arteriolar lesions are the consequence of the hypertension, and it has been shown that if the blood pressure can be lowered significantly the malignant phase of hypertension, whether essential or renal in origin, may be converted into the benign one with retrogression of the retinal changes, improvement in the electrocardiogram, and presumed healing of the arteriolar necroses, with a considerable improvement in the survival rate. Good results have been reported from treatment with hexamethonium or the rice or low-sodium diets, and from surgical treatment such as sympathectomy, removal of a phaeochromocytoma or non-functioning kidney, or adrenalectomy. Morrissey, Brookes, and Cooke[5] reported a striking increase in survival time after sympathectomy in cases of malignant or progressive hypertension, and pointed out that marked subjective and objective improvement may sometimes be seen even if the blood pressure does not fall much after operation.

In the opening pages of the *Journal* this week Dr. Brenda Morrison reports her results in a similar series of patients treated with parenteral hexamethonium. Five of her thirty-nine patients died during treatment, in four it was deliberately discontinued, six gave up treatment, and twenty-four continued with regular treatment. The results in this last group are impressive, for many were severely ill and steady deterioration would have been expected. Eighteen of the twenty-four patients treated for from three to fifteen months were able to lead practically normal lives, and the remainder were all much improved. A significant fall in both systolic and diastolic pressures was obtained, the degree of papilloedema diminished rapidly in every case of malignant hypertension, the electrocardiogram and signs of congestive failure were improved, and headaches usually disappeared. It is too soon to assess the effect of this form of treatment on survival time, particularly in view of the late occurrence of unusual pulmonary changes, but the immediate results are excellent.

The difficulties of hexamethonium treatment are well illustrated in this paper and in the accompanying one written in conjunction with Dr. W. D. M. Paton. A close study of these papers should discourage the indiscriminate or casual use of these drugs. Control of blood pressure with oral hexamethonium is unsatisfactory in most cases, and oral treatment might well be reserved for those cases with severe headache but without objective evidence of vascular degeneration in the hope that later remission of this symptom might occur. Morrison, and also Smirk and Alstad,[6] have shown that adequate control of blood pressure even in severe cases can be obtained with parenteral hexamethonium, but the difficulties in controlling this

[1] Bechgaard, P., *Acta med. scand.*, 1946, Suppl. 172.
[2] *Amer. J. Med.*, 1950, **8**, 53.
[3] *British Medical Journal*, 1953, **1**, 1131.
[4] Pickering, G. W., *et al.*, *Lancet*, 1952, **2**, 952.
[5] Ibid., 1953, **1**, 403.
[6] *British Medical Journal*, 1951, **1**, 1217.

method of treatment with a potentially dangerous drug are such as to limit its general use. The variable response to the initial doses and the development of tolerance necessitate close observation during the early stages, and the treatment demands a degree of co-operation by the patient for an indefinite period which will not often be easy to obtain. When secondary vascular changes have occurred and steady deterioration is to be expected, inadequate medical treatment will be disastrous, and then sympathectomy with its known good results in this type of case will probably be the treatment of choice for most of such patients. The use of parenteral hexamethonium as pre-operative preparation for surgery has been insufficiently explored, but it might well be that two to three months' intensive treatment on the lines described by Morrison followed by sympathectomy would give results better than with either method used alone.

The use of the ganglion-blocking drugs such as hexamethonium in the treatment of hypertension has stimulated the search for other drugs which will avoid the obvious difficulties and disadvantages of hexamethonium treatment, and it is to be hoped that an efficient oral preparation will become available. Meanwhile it is well to remember that cases of malignant or rapidly progressive hypertension form a very small proportion of the total hypertensive population, and it is only for these relatively few patients that drastic medical or surgical treatment is indicated.

DISEASE, RACE, AND CIVILIZATION

Medicine as it is known and taught to-day is largely concerned with disease in the civilized white man. When the world is considered as a whole the white men are a minority group, and civilized man is a recent phenomenon in history. The study of little-known races living in primitive environments in medically unexplored territory can be expected to reveal new manifestations of disease, if not new diseases, which may well prove important in the general advance of medical knowledge. Further study of the differences in the incidence of appendicitis in different West Indian island populations,[1] for instance, might clarify the aetiology of this condition. It is especially important that such work should be done now, since primitive ways of life and even the people themselves are in danger of dying out.

Structural differences between peoples probably play some part in determining the racial incidence of disease. Thus the tendency of the Negro to develop umbilical hernia has been ascribed to the frequency among negroes of the " skin " type of umbilicus with a tubular projection of the peritoneum into the umbilical cord.[2] The wide nasal cavities of negroid and mongoloid peoples seem to be associated with a diminished incidence of infective and obstructive diseases of the ears, nose, and throat. Racial variations in the anatomy of the teeth[3] and of the mastoid process influence surgical methods. The pigmented skin of the Negro protects him from the effects of the sun's rays in causing sunburn and skin cancer, which is common in albino Negroes.

The racial incidence of disease is sometimes due to quite simple genetic differences between peoples. This is the case in haemolytic disease of the newborn, which does not occur in those Oriental people who are entirely Rhesus-positive, and also in Cooley's anaemia and sickle-cell anaemia.[4] Variations in susceptibility between races are found in many other diseases, but whether they are due to genetic or environmental causes remains obscure. Primitive communities from four continents have been found to be almost completely free from hypertension, for instance, the blood pressure remaining stationary or falling with advancing age.[5]

Racial variations in neoplastic disease lie mainly in the frequency of different types of tumour. Quaint habits, such as smoking cigars with the burning part inside the mouth, and walking about with a firepot pressed to the belly, are responsible for some of these differences, and others are due to more obscure environmental influences. There is some evidence for a predisposition to cancer of those organs, notably the liver, which are affected by kwashiorkor, a disease which occurs in populations whose traditional dietary habits have been disrupted by the production of cash crops.[6]

The problem of race and infectious disease has been extensively reviewed by Perla and Marmorston.[7] No example of racial immunity to an infectious disease is known in man, though examples of this occur in some domestic breeds of animals. Different populations do, however, show widely different mortality rates when attacked by infectious diseases. The nearest approach to racial immunity seems to be the

[1] Leacock, A., *British Medical Journal*, 1952, **1**, 1347.
[2] Jeliffe, D. B., *Trans. roy. Soc. trop. Med. Hyg.*, 1952, **46**, 428.
[3] Tratman, E. K., *Dent. Rec.*, 1950, **70**, 63.
[4] *British Medical Journal*, 1952, **1**, 426.
[5] Polunin, I., ibid., 1952, **1**, 1190.
[6] Trowell, H. C., *Nutr. Rev.*, 1950, **8**, 161.
[7] *Natural Resistance and Clinical Medicine*, 1941, Boston, pp. 31–126.
[8] Editor, *Rasse und Krankheit*, 1937, Munich.
[9] Gelfand, M., *The Sick African*, 1948, 2nd edition, Capetown.
[10] Lewis, J. H., *The Biology of the Negro*, 1942, University of Chicago Press.
[11] Bertelsen, A., *Meddelelser om Grønland*, 1940, **117**, No. 3.
[12] Snapper, I., *Chinese Lessons to Western Medicine*, 1941, New York.
[13] Cleland, J. B., *J. trop. Med. Hyg.*, 1928, **31**, 53 et seq.
[14] See Edge, P. G., *Vital Statistics in the Tropics*, 1947, London.
[15] Tropical medical exploration and survey work is reviewed in the section on Reports, Surveys, and Miscellaneous Papers in the *Tropical Diseases Bulletin*.
[16] McGregor, I. A., and Smith, D. A., *Trans. roy. Soc. trop. Med. Hyg.*, 1952, **46**, 403.

lack of the scarlatinal response in the American Indian and the Malaysian peoples.

Infections usually cause a high mortality in populations which have never before experienced them, and introduced infectious diseases have probably been the greatest cause of depopulation among primitive peoples. Further exposure may lead to an increase of resistance among the population by the action of natural selection. Lack of nursing care and starvation are, however, important causes of this high mortality. Since common infectious diseases tend to be diseases of children whereas newly introduced epidemics affect all ages, apparent racial differences in susceptibility may be due to age variations in susceptibility. Thus the susceptibility of virgin races to tuberculosis is partly due to the seriousness of the primary disease in adults, and the apparent immunity to yellow fever of the Negro from endemic areas in Africa may be due to the mildness of yellow fever in childhood. The partial immunity to malaria of rural tropical communities is probably acquired at the cost of a grave mortality in childhood which is difficult to detect where medical services are rudimentary.

The student of race and disease should consult Schottky's book[8] on that subject, though much of the information is anecdotal, and many of the opinions expressed are those which were current in Nazi Germany. Detailed accounts are available of the diseases of the African[9] and the American Negro,[10] the Eskimo,[11] the Chinese,[12] and the Australian aboriginal.[13]

It is easy for the medical practitioner working in the " back of beyond " to feel that he is stagnating in his isolation, and yet it is not difficult for him to produce really valuable researches. He can study a particular disease, collect vital statistics,[14] or make a disease survey.[15] These can give valuable information to governments in pointing out the true medical and nutritional needs of the people. Medical survey work should ideally be carried out in conjunction with workers in other fields, such as physical and social anthropology, agriculture, and nutrition. The main requirements are adequate description of the methods and descriptive criteria used, sufficient background information on the people studied, and the collection of data in a systematic manner. Work of this sort is being carried out on isolated African populations by the M.R.C. Field Research Station in the Gambia[16] and on Malayan aborigines by the University of Malaya. In these days of air transport, lack of laboratory equipment and skills can often be overcome by sending specimens to acknowledged world experts, who may be only too glad to have this opportunity of carrying their researches into new fields.

DOCTORS ON EVEREST

The climbing of Everest is a triumph already acclaimed wherever the victories of the human spirit are prized above those of the market-place. The silent challenge of its peak has attracted eleven expeditions—not all intended to gain the summit—and sixteen lives have been lost in meeting it. If courage and resource are the qualities pre-eminently needed to explore those wastes of rock and snow, solutions to the physiological problems of living strenuously at high altitudes were no less necessary to the success that added a further touch of splendour to Coronation Day.

Medical men have contributed much to make these expeditions possible at all, both in helping to design suitable equipment and in accompanying, and sometimes leading, the climbing parties; they have also to carry out the essential but less spectacular duties of looking after the members of the expedition in the long approach to the mountain. The doctor in medical charge of the expedition, besides advising on camp hygiene, may have to deal with almost any medical or surgical emergency in one of the most remote parts of the world, from setting a broken limb to treating heatstroke or frostbite. His is the duty also—a familiar one to regimental medical officers during the war—of looking out for early signs of the mental disturbances that can have such serious consequences if allowed to develop and spread among strained and tired men. In giving advice on acclimatization the experience of a mountaineer-doctor is invaluable to the leader of the expedition. At Himalayan altitudes, and especially above 20,000 ft., the benefits of becoming acclimatized are apt to be offset by a deterioration in health whose cause is not clearly known. Individuals vary greatly in their response to these stresses, but after a time nearly everyone suffers a diminution of nervous control and a loss of weight which may be severe. There are in addition the hazards of a violently fluctuating temperature, which specially designed equipment can only partially mitigate. Bright sunlight by day may cause heavy sweating, to be followed by sub-zero temperatures at night, and perhaps even more difficult to overcome than the low oxygen tension is the dehydration that these altitudes cause.

The doctors accompanying this year's expedition have indeed earned the plaudits of the profession.* The medical officer in charge is Dr. Michael Ward, who qualified at the London Hospital in 1949, and gained his first experience of Himalayan climbing in the 1951 reconnaissance expedition. Also on medical work, though as a physiologist, is Dr. L. G. C. Pugh, a member of the Medical Research Council staff and, during the war, physiologist to a mountain and snow warfare training centre. The third medical member is Mr. R. C. Evans, who was chosen to accompany the expedition primarily for his climbing experience, much of which has been gained in the Himalayas. He and T. D. Bourdillon, whose father, Dr. R. B. Bourdillon, had constructed an experimental closed-circuit oxygen apparatus for the expedition, were the first to attempt the summit this year, reconnoitring a route with the new apparatus.

*See telegram (p. 1341) sent by Chairman of B.M.A. Council.

Though they failed to reach the top with it, they have the satisfaction of being indispensable members of a team whose efforts have met with success. And it is a team comprising not only the climbers now out there but those many who have tried their fortune on the mountain previously, for they brought back that information and advice—again much of it medical—which were the foundations on which Colonel Hunt's men, with trust and daring, built their success.

TOXIC EFFECTS OF PHENYLBUTAZONE

The use of phenylbutazone ("butazolidin") for the relief of pain in rheumatoid arthritis and osteoarthritis raises problems which are described in detail in the papers by Drs. J. R. Nassim and T. Pilkington and by Dr. J. C. Leonard on pages 1310 and 1311. Reports on the use of phenylbutazone make it clear that the drug can be used with benefit, certainly so far as the relief of pain is concerned, and that in this respect it is more effective than aspirin, either alone or in the usual mixtures. But phenylbutazone has toxic effects, and these have led Dr. Leonard to conclude that it should be given only to patients in hospital. Some recent papers published in the United States[1] add to the evidence on the serious accidents that may result from phenylbutazone therapy. One patient aged 54 received 400 mg. by mouth daily for one week; he was then put on 600 mg.; nine days later there was a perforation of the first portion of the duodenum. In other patients there was bleeding from ulcers during the use of phenylbutazone, and another patient died from agranulocytosis. The formula of phenylbutazone is sufficiently similar to that of amidopyrine to make it likely that cases of agranulocytosis will from time to time occur.

The incidence of toxic effects has varied very much with different observers, from 1.8% to 52%. How is this variation to be explained? It is difficult to suppose that those who have noted few toxic reactions have missed effects which were serious or dangerous to their patients, but it is reasonable to suppose that they have overlooked effects which were not serious. On the other hand perhaps those who have described a high proportion of toxic reactions have included minor disturbances some of which the patients themselves might not have reported. It seems probable that the variation in the incidence of toxic symptoms is a reflection of the difference in the observers or in the conditions of observation. If so, too much attention should not be paid to the percentage of toxic reactions as an indication of the risks of using the drug.

Toxic reactions in a minority of patients may be set aside as an inevitable disadvantage of any substance foreign to the body, and doctors may decide to use a remedy in spite of them. The matter is usually decided by the doctor's own experience with the remedy, and if he sees no ill effects in his first fifty patients he will be likely to blame the patient rather than the remedy when the ill effects are seen in the fifty-first. As reports of serious toxic disturbances accumulate, so the time may come when no one will be willing to use the drug for the first time. Only those doctors will give it who have already found it to be beneficial and who have not yet observed toxic effects.

Many of the patients for whom phenylbutazone is prescribed are old and have suffered for many years. On general grounds they would seem more likely to show toxic symptoms than younger people, since their detoxicating mechanisms, in particular those of the liver and kidney, are less efficient, and the blood-forming apparatus is more sensitive to attack. Should a doctor refuse to use a remedy which gives relief to a majority of such patients because it causes side-effects in 20% of them? One answer to this is that the doctor should use it only if he is satisfied that he has sufficient opportunity of keeping the patient under supervision. Another answer is that he should refuse to use it and wait until the pharmaceutical firms have produced less toxic remedies. That this may be possible is evident from the success of mepacrine, proguanil, and pyrimethamine against malaria. All are remarkably non-toxic, though they are substances foreign to the body.

[1] *J. Amer. med. Ass.*, 1953, **152**, 28.

INFLUENZA AS A WORLD PROBLEM

The first report[1] of the World Health Organization's Expert Committee on Influenza, just published, contains a lucid account of the present state of knowledge about influenza, and where opinions conflict or information is incomplete it frankly says so. The Committee met in Geneva last September and consisted of nine members from six different countries. Though there is a place for independent research on many and various aspects of influenza, there are fields where international collaboration is needed and where progress will be difficult without it. For instance, we read that "recent studies . . . have shown two possible methods by which epidemics may be originated. Geographical spread of virus from one country to another has been indicated in some studies, but others rather favoured the development of an epidemic from an endemic state." In fact, there is increasing evidence that the "two possible methods" are not mutually exclusive but that both operate. Here is one important field where countries can help each other to discover how the common enemy, influenza, conducts its campaigns. Influenza viruses, more than any other, vary from year to year: newly emerging antigenic variants appear and may cause trouble when they find a population relatively susceptible. This variability makes it more difficult to be prepared with appropriate vaccines. On the other hand, we can follow the distribution and spread of new antigenic types and thus perhaps learn more about influenza's secret operations than if it were a wholly stable entity. The report describes the methods used in different laboratories for comparing the strains of virus which turn up. Were there more uniformity among these methods, more might be learnt sooner on this difficult subject.

The report gives sound recommendations on how material for study can be collected and distributed, and how information on outbreaks of influenza can be quickly gathered and made available. Two appendices

[1] *Wld Hlth Org. techn. Rep. Ser.*, No. 64. 1953.

give details of methods in current use for preparing antisera of various kinds and for performing serological tests, both haemagglutination-inhibition and complement-fixation.

Much has been done since W.H.O. set up in 1948 the World Influenza Centre in London and helped to organize collaboration throughout the world; but clearly much remains to do. On the immediately practical questions of control the report has much of interest. Vaccines are discussed and the difficult question of what strains of virus to incorporate in them. There seems to be great hope for the future in the use of vaccines containing oily adjuvants. These are likely to give a stronger, more durable, broader antigenic response than has been possible before. But more knowledge is required about their safety before they can be generally recommended.

Influenza to-day causes great economic loss and kills many of the old and infirm. But its ravages are trivial compared with those of the lethal pandemic of 1918–19. Now we study vaccines, therapy, quarantine, and so forth partly for our immediate needs but even more because we do not know whether another killing influenza may not come upon us nor when it may do so. Because there are at present no indications of such a calamity we must not be lulled into unpreparedness; it is as well that the Expert Committee is aware of the danger and is not too complacent about the efficacy of antibiotics. What the report has to say about quarantine measures is worth quoting:

> "Quarantine at a national level would be likely to be effective only in the case of islands and geographically isolated communities. The role of quarantine in regard to large countries or continents cannot be assessed while knowledge concerning the spread of influenza is still imperfect. There is no evidence, however, that in the case of such large areas quarantine could be applied effectively. The probable value of restriction of travel between countries can be judged in the light of the above remarks; and particularly in the case of mild epidemics of influenza, it is totally unjustified."

At the modest price of eighteen pence the report should prove a good investment for many people interested in what is referred to as "one of the most important infectious diseases still unconquered."

PUBLIC HEALTH AWARD

The salary increases awarded by the Industrial Court to assistant medical officers in the public health service are not all that was asked for, but at least they are substantial. They indicate some recognition of the increased cost of living that has so harassed professional people since the war, and bring the salaries into better relation with those earned both in the public health service and in comparable posts outside. The minimum salary in the scale is raised £100 from £850 to £950, and the maximum goes up £150 from £1,150 to £1,300. Medical officers at the maximum of the old scale and therefore earning £1,150 are to go immediately to £1,250 on the new scale and thence to the new maximum of £1,300; while officers at other points go to the corresponding points on the new scale. The award takes effect from June 1.

Fuller details of the award, which are reported in the *Supplement* at page 278, show that, while it falls short of the profession's claim by £50–£100, it is a considerable advance on what the Management Side of the Whitley Committee "C" was offering. That was a kind of cost-of-living allowance adding £25 to the minimum salary and tapering off until the same maximum salary was reached after the same number of increments. The niggardly character of this offer must have been as evident to the Industrial Court as it was to the medical officers concerned, and the award bears no trace of being influenced by any part of it. The scale claimed by the medical officers represented a 100% increase over the pre-war scale. In comparison with many other claims, especially those outside the professions, it was therefore a modest one. Even so, the Court did not see fit to decide wholly in its favour. But it should do much to mitigate the hardship of which some assistant medical officers have justly complained in recent years.

THE PAINFUL SHOULDER

In 1934 Codman[1] drew attention to the degenerative changes which occur in the conjoined tendon of the supraspinatus, infraspinatus, teres minor, and subscapular muscle. These changes affect the supraspinatus tendon more frequently than its neighbours. They are common in women at the menopause and in men with cardiovascular disease, and are the essential precursors of painful lesions of the shoulder. These were discussed by Withers in our Refresher Course series last year.[2]

The painful shoulder syndrome may be started off by occupational strains and minor injuries, particularly those causing partial tears of the supraspinatus tendon, by immobilization for such conditions as fractures of the arm and operations on the breast, and by pain referred from the cervical spine. Another factor is what Coventry[3] calls the "peri-arthritic personality." This comprises undue sensitivity to pain and certain constitutional and emotional characteristics common in patients with stiff and painful shoulders.

Two chief clinical lesions are recognized: the local tendinitis, usually confined to the supraspinatus tendon, and the diffuse capsulitis of the conjoined tendon. In cases of local tendinitis movement may be only slightly impaired, but there is pain in the mid-range of abduction when the supraspinatus tendon impinges on the acromion—the "painful arc syndrome." In cases of diffuse capsulitis gross restriction of movement is common—the "frozen shoulder." Pain may be severe in the early stages, but as movement diminishes the pain subsides. In severe examples of this type pain may radiate down the limb to the hand, and there may be swelling and stiffness of the fingers, giving what is described as the "shoulder–hand syndrome."

Radiological examination may reveal the presence of a calcified deposit. These deposits usually lie in the substance of the supraspinatus tendon, but may occasionally invade the subacromial bursa. Deposits confined to the tendon commonly produce the symptoms of a

[1] *The Shoulder*. Boston, Massachusetts: T. Todd. 1934.
[2] *British Medical Journal*, 1952, **1**, 40.
[3] *J. Amer. med. Ass.*, 1953, **151**, 177.
[4] *J. Bone Jt Surg.*, 1949, **31B**, 436.
[5] Ibid., 1949, **31B**, 433.

tendinitis, although they may be quite symptomless. The sudden onset of severe pain, swelling of the shoulder, and pyrexia are usually indications of a bursitis.

The painful shoulder is notorious for its discouraging response to treatment, but fortunately there is a strong tendency towards spontaneous although slow recovery. In cases of local tendinitis it is important to avoid movements that produce pain and to preserve joint motility by gentle active exercises. When disability is severe an abduction splint should be used during the day. Radiant heat and diathermy are often administered, but not always very effectively. Acromionectomy as described by Armstrong[4] may be required if symptoms persist. This operation will often reveal inflammatory changes in the subacromial bursa and unsuspected tears of the supraspinatus.

In the active painful stage of capsulitis rest in a sling is advisable and exercises should be of the "pendulum" type or with the patient in the supine position and the arm supported. For the painless frozen shoulder exercises should be vigorous. Manipulation under general anaesthesia is contraindicated during the painful phase, but may be indicated for the frozen shoulder when progress with active exercises ceases. A.C.T.H. and cortisone have been administered, chiefly during the painful active stage. Rapid increase in the range of movement and relief from pain have been reported. Further clinical trial will be required in order to establish the proper place of these hormones in the therapy of the painful shoulder.

Calcified deposits in the substance of a tendon do not often need removal, for they frequently absorb spontaneously, but when there is a bursitis with severe pain immediate relief can be obtained by evacuation of the bursa through a short muscle-splitting incision. There is undoubtedly a place for this small operation, although, as Blundell Jones[5] has shown, the bursitis will subside in time with conservative treatment.

DR. BROCK CHISHOLM'S ADIEU TO W.H.O.

Exceptional qualities are called for in the chief administrative officer of an international organization. He must be not only its servant but in a sense its master, not only carry out its decisions but to some extent initiate and ensure them; he must be not only a Civil Servant but a principal in world affairs. The United Nations has been fortunate in the men who have occupied the principal posts in its specialized agencies, conspicuously so in the World Health Organization, which from its start in 1946 has had Dr. Brock Chisholm as its Director-General. Dr. Chisholm, who is still the right side of 60, is retiring from the post, and no doubt has further achievement in other important spheres in front of him. He was well chosen, for he had been Director-General of Medical Services in the Canadian Army and Deputy Minister of National Health and Welfare in the Federal Cabinet, and before he held those posts he had been for seven years in general medical practice in Toronto, a period which was both preceded and followed by a year or two of postgraduate work in London.

In his farewell address delivered to the recent sixth World Health Assembly Dr. Chisholm spoke of the conditions essential to the success of the Organization, insisting that the first of them was the participation of all nations in the work of W.H.O.

"The whole concept of this Organization, all the principles included in its constitution, are based on this simple truth: in our shrunken world, health, like peace and security, is indivisible, and mankind's fight against illness, its major enemy, can be won only through the concerted effort of us all."

There has been some girding at the cost of what are sometimes called United Nations "frills." Even in the old days of the League, whose building at Geneva W.H.O. inhabits, the health budget was a favourite target for criticism, not least among the delegates themselves, who spent many a midnight devising cheeseparing economies. Yet, as Dr. Chisholm pointed out, the expenditure through W.H.O. is no more than the amount which many a large city spends on its municipal sanitary arrangements. Seen against the background of need in a world where most people are still without the benefits of modern medical knowledge, the W.H.O. budget is ridiculously small. The contribution of the United Kingdom, so far as we can make it out, is about one penny a year for each citizen. The world has been slow in realizing that health—and not on humanitarian grounds alone—is an international concern. It is true that there have been recent upsurges, such as Point IV and the Colombo Plan, but, while it has been proclaimed that nations must be prepared to invest an important part of their resources in banishing economic and social insecurity which give rise to the fear of war, the impulse has been bedevilled because this very fear of war gives an overriding priority to rearmament and prevents governments from embarking upon the rehabilitation of the under-developed areas. Nevertheless, W.H.O. has achieved much in seven years in the control of communicable diseases and in the encouragement of national health projects. But most of all, as Dr. Chisholm said, it has afforded evidence, along with other agencies of the United Nations, that men belonging to widely different political, social, and religious systems can co-operate in fraternal association.

Dr. Chisholm concluded his address with a warm tribute to Switzerland and the canton and city of Geneva, the ideal "host Government," which has been helpful in every respect, but has never attempted to influence policies or attitudes. He leaves the service with a greatly enriched experience, with the record of a job well done over seven strenuous years, and with friendships firmly established in nearly all countries, not least among the members of the World Medical Association, at whose assemblies he has been a welcome observer and guest. His successor[1] is Dr. M. G. Candau, of Brazil, who is well fitted by training and experience to this important office. Educated at Rio de Janeiro and the Johns Hopkins University, Baltimore, he had a distinguished career in the public health service of Brazil and served on the W.H.O. staff in 1950–1. He now leaves the Pan-American Sanitary Bureau to take up his new appointment.

1 *British Medical Journal*, 1953, 1, 345.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

INTERMITTENT CLAUDICATION

BY

J. B. KINMONTH, M.S., F.R.C.S.

Assistant Surgeon and Assistant Director of Professorial Unit, St. Bartholomew's Hospital

The term "intermittent claudication" is derived from the latin *claudicare*, to limp or halt, not as is sometimes thought from *claudere*, to shut, a derivation which would suggest an erroneous explanation for the symptom by implying that the blood vessels to the limb were subject to intermittent episodes of closure. In fact the symptom is caused in most cases by thrombosis in a segment of a main artery. The collateral circulation past the thrombosis supplies enough blood for muscles at rest but too little for the increased needs during exercise. The thrombosis may originate from injury to the vessel by violence or it may start upon an area of disease in the intima such as an atheromatous plaque. Atheroma is by far the commonest cause of arterial thrombosis at all ages. It is a much more serious lesion than fibrosis or calcification of the tunica media, which may make vessels feel hard to palpation and opaque to *x* rays but do not themselves cause thrombosis.

Claudication is a painful symptom and therefore alarming to the patient. Usually it does not itself prove a great handicap, and its importance lies more in the other changes in the limb or cardiovascular system that may accompany it. Its treatment, therefore, is almost always incidental to measures planned to improve the circulation in the limb as a whole.

Diagnosis

A carefully taken history is the most important element in diagnosis. No condition other than arterial insufficiency exactly reproduces the sequence of pain after a definite period of exercise relieved by resting and reproduced constantly by the same amount of exercise. Even when the patient also has pain at rest it is usually described as being different in nature from the pain brought on by exercise, and is usually situated in the foot or ankle rather than the leg. Patients with osteoarthritis may complain of pain on exercise, but it is usually worse on starting and wears off with continued movement. Muscular rheumatism or fibrositis may sometimes cause confusion, but the history is never exactly the same, particularly in that it comes in attacks or episodes and is variable, unlike true intermittent claudication. Other symptoms of peripheral ischaemia such as coldness, numbness, or paraesthesiae in the limb and even ulceration or necrosis may coexist and give confirmatory evidence in the diagnosis.

The most valuable part of the clinical examination is palpation of the pulses. In normal people femoral, popliteal, and two ankle pulses can be felt, but in about one subject in ten the dorsalis pedis pulse is absent. Some difficulty may be experienced in feeling the popliteal pulse in fat patients. Should it be impalpable by the usual method with the knee flexed to a right-angle an alternative method can be used with the knee hyperextended on the couch.

Most patients with claudication have no palpable pulses below the femoral. Very rarely a patient is found with normal pulses and no physical signs of disease in the limbs despite a definite history of intermittent claudication. Usually he is a young man who can walk a quarter of a mile (half a kilometre) or more before pain occurs. Arteriography is necessary in such a case to confirm the diagnosis, and mural thrombosis or a very short segment of complete obliteration is the usual finding. Apart from such exceptional cases no special methods are necessary in the diagnosis of peripheral arterial disease other than those of history-taking and clinical examination.

Conservative Treatment

Thrombosis may occur in a main peripheral artery and give rise to acute symptoms resembling those of embolism, with pain, pallor, and coldness in the foot, but usually it occurs insidiously with few if any symptoms other than the onset of claudication. After the initial stabilization of the circulation a much slower hypertrophy of the collateral vessels takes place, leading to an improvement in the walking distance which may occur over weeks or months. This later spontaneous improvement in blood flow occurs with conservative treatment in many cases, and is the probable explanation of the claims made for various forms of treatment of doubtful efficacy. It is therefore a good rule to allow ample time for this natural improvement to take place, aided by conservative measures, before contemplating more radical ones. In cases in which claudication is the chief or only symptom operation should not be considered until the symptoms have become constant and stationary for three to six months.

Cardiovascular Assessment.—Peripheral arterial obstruction other than that due to trauma is almost always part of a general disease affecting other parts of the body. The heart may be affected, and so its condition must be investigated and any necessary treatment given. If operation is considered it must be decided not only whether the patient is fit for it but whether it will be of benefit for him to walk further. It would be an unhappy sequence for a patient to be cured of claudication only to experience angina pectoris because of his ability to walk further. Evidence of cerebral arteriosclerosis must also be taken into account in deciding treatment.

Diet.—There is evidence that in both man and animals a high intake of fat and lipoids in the diet tends to cause the development of atheromatous lesions in the arteries. It has not, however, been shown that omitting fat from the diet will check further progress of the disease once it has started. If the patient is obese he should be put on a low-calorie diet with the immediately practical object of giving his ischaemic legs less weight to carry rather than in any more ambitious hope of stopping further development of the disease.

Vasodilator Drugs.—The most generally useful is tolazoline hydrochloride ("priscol"). It is given orally in doses of 50 mg. thrice daily. If side-effects such as giddiness or nausea occur the dose is reduced to 25 mg. three times a day.

Smoking and Alcohol.—There have been many attempts to prove that some of the acute forms of arterial obliterative disease are caused by sensitivity to tobacco, but they have not met with general acceptance. There is, however, ample proof that smoking has a constrictor effect on peripheral vessels, leading to temporarily diminished blood flow even in normal subjects. This is due both to overbreathing and to the effect of the tobacco itself. For this reason alone patients with peripheral arterial disease should be advised to give up smoking. Alcohol, on the other hand, is a good peripheral vasodilator and a moderate regular intake is helpful. The patient who is disconsolate at the loss of the one minor vice may be cheered by the retention of the other.

Buerger's exercises, in which the patient elevates the limb for half a minute, holds it horizontal for a minute, and then dependent for a minute, should be done three times and repeated three times a day. They are designed to stimulate the collateral circulation.

General Care of the Feet.—Patients with intermittent claudication very often have deficient circulation in the skin, so that the feet need to be particularly cared for. Minor injuries may lead to indolent ulcers or infection which may further injure the circula-

tion and cause necrosis or gangrene. Shoes must be comfortable and kept in good repair so that friction and blistering or injury by projecting nails never occur. If a chiropodist is available regular visits are advisable; if not the patient himself must be careful when cutting his nails not to injure the soft tissues. The toe-nails are best cut immediately after a bath, when they are soft and unlikely to splinter or leave sharp projections. Interdigital fungus infections are dangerous because they make excoriation

FIG. 1.—Palpation of the popliteal pulse by the flexed knee method.

FIG. 2.—Palpation of the posterior tibial pulse behind the medial malleolus.

and infection likely. A good prophylactic regime is the routine use, after bathing, of 1% salicylic acid in surgical spirit followed by the application of zinc oxide and salicylic acid dusting powder (*N.F.*, 1952), paying particular attention to the interdigital clefts. In order to maintain as much circulation in the feet as possible the patient must at all times keep himself and his feet warmly clad and particularly avoid getting his feet wet and cold. Hot baths are good because they produce reflex vasodilatation. The feet should be kept out of the hot water at first until reflex vasodilatation is caused by the rest of the body warming up: direct application of heat to tissues may increase their metabolic demands beyond the capabilities of supply by a sluggish circulation. The same principle applies in bed. The bed should be warmed and bed-socks worn, but a hot-water bottle is better applied to the trunk than to the feet.

Exercise.—In those cases in which thrombosis has occurred as an acute episode complete rest in bed will be necessary until the circulation is stabilized. Later on in these cases, and in others in which intermittent claudication has followed insidious thrombosis, advice will be needed on how much or how far the patient should walk. Moderate exercise is beneficial, as it provides some stimulus to the collateral circulation, but the patient should stop before or on the onset of the least discomfort. He should not persist until the onset of actual pain, for this may cause tissue damage by ischaemia.

The details of conservative treatment conscientiously followed often prevent the deterioration or loss of a limb. They should be carefully explained to the patient, who should know that successful treatment and perhaps the fate of the limb depend largely upon his own efforts. In cases in which operation is necessary the same care must continue afterwards. Few, if any, surgical measures can restore the circulation to normal.

A number of methods of treatment have been advocated which have been popular from time to time but which need complicated apparatus or an amount of skill, time, and trouble out of proportion to the benefit achieved; some of them carry a disproportionate risk. In this group or in its boundaries lie such methods as intermittent venous occlusion, repeated spinal anaesthetics, caudal blocks and paravertebral blocks, and repeated intra-arterial injections of vasodilators. So-called chemical sympathectomy is of value in certain cases. Old or decrepit patients unfit for general anaesthesia may benefit, but more often when the chief symptom is pain at rest or impending necrosis rather than intermittent claudication. It is done by injecting a few millilitres of 5% phenol around the lumbar sympathetic chain.

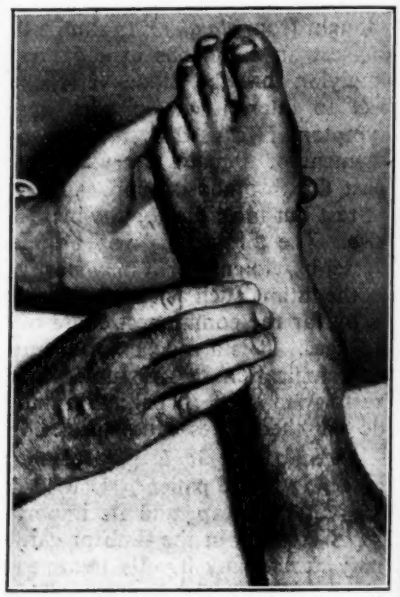


FIG. 3.—Palpation of the dorsalis pedis pulse.

Sympathectomy

Sympathectomy is the most generally useful operation for patients with peripheral arterial disease. It improves the blood supply by dilating collateral vessels. The effect is more pronounced in the skin than in the muscles of the limb, and usually only those patients with the less severe forms of claudication have their symptoms abolished. The best results are achieved in patients whose pain does not halt them completely but allows further progress at a reduced pace. Many patients with claudication also have impaired circulation in the skin, which is more important because of its influence on the fate of the limb. This is considerably and permanently helped by sympathectomy and is often the primary indication for operation. Pain in the foot at rest, provided there is no area of necrosis or gangrene, responds well to sympathectomy and is not a contraindication to the operation.

The sympathetic chain and ganglia lying on the bodies of the second, third, and fourth lumbar vertebrae are removed. Excision of the first lumbar ganglion is unnecessary in most cases: it may have the disadvantage of hindering sexual function by interfering with ejaculation. The old operation of periarterial sympathectomy has been abandoned, as has also arteriectomy of the thrombosed segment, except in those cases in which the artery is superficially placed and causing pain.

Tenotomy

It has been found that inactivation of some of the leg muscles often enables a patient to walk further before the onset of pain. The most probable explanation for this is that the demand for blood during exercise is reduced. Division of the Achilles tendon inactivates the gastrocnemius

and soleus muscles, leaving the remaining calf muscles for the patient to walk with. Naturally there is some loss of power and the patient is less agile in ascending stairs or in any action requiring vigorous plantar flexion. For this price a marked improvement in walking distance may be gained. The strongest indication for tenotomy is claudication in one limb after walking a short distance, thirty to forty yards (30 metres) perhaps, in an older patient with relatively good skin nutrition. Many patients require sympathectomy either before or at the same time to improve skin nutrition, but this is not always so and tenotomy may be done as an isolated procedure. A good pre-operative test of the possible effect of tenotomy on a patient with one-sided pain is to raise the heel ¾ in. (2 cm.) by placing a felt pad under it. If this increases the walking distance tenotomy is likely to improve it further still. Sometimes the improvement after the heel has been raised is so pronounced that it may be permanently raised, thereby making operation unnecessary.

Bilateral tenotomy may be needed in patients who have pain in both legs after walking a very short distance. The operation can be done under local analgesia as an open or closed procedure. In either case pre- and post-operative ankle exercises must be taught and carried out, and the patient made to start walking within 24 hours to avoid the risk of thrombosis in the veins of the calf muscles. Other means of inactivating muscles in the leg, such as neurotomies, have been tried, but they are less certain, less effective, and often more extensive procedures than tenotomy. They have now been given up.

Reconstructive and Other Operations

In theory the ideal way of treating arterial obliteration is by replacement with some form of tube to conduct the blood. It is possible in practice to treat a small number of patients in this way. The problem has two aspects: that of the material to be used, and that of the choice of patient who may be helped.

Material for Grafting.—At present the material of choice is an arterial homograft. This is a vessel which has been taken under sterile precautions from the body of another person recently dead. Death must have been due to some cause other than infection, and the best material comes from young subjects who have had fatal accidents. The grafts are rapidly frozen to −79° C. and banked at this temperature, which preserves them for long periods in a state ready for use. The second choice is a vein autograft —that is, a vein taken at operation from the patient himself. The great saphenous is the vein usually used. This is a good method for use in war, as no extra organization for storage or supply is needed. It is not so useful in replacing defective arteries larger than the popliteal because of the discrepancy in size, and it is more difficult to anastomose to a thickened arteriosclerotic vessel than an arterial graft would be. Other materials are unsuitable for various reasons. Arteries from the patient himself cannot be spared, nor can veins larger than the great saphenous be used without causing disability. There is still no way of proved safety for preparing heterografts—that is, arteries from different animal species—and the same applies to the various plastic and cloth tubes which have been tried under experimental conditions.

Choice of Patient.—The small group of patients suitable for treatment by grafting consists of those in whom the obstruction is enough to produce marked claudication or necrosis, but in whom the disease is relatively localized in the arterial tree. A number of patients are excluded on general clinical grounds because of cardiac, cerebral, or diffuse disease elsewhere in the body. Others are found to be unsuitable on arteriographic evidence of extensive disease in the arteries of the limb. In others, particularly those with a short block, good collaterals, and mild symptoms, grafting is unnecessary because they do well with less radical treatment, such as sympathectomy.

Thrombo-endarterectomy.—Another method of restoring patency to thrombosed arteries which is occasionally useful is that known as "thrombo-endarterectomy" or "désobstruction." Here a longitudinal incision is made in the vessel wall and the clot removed together with the intima and part of the media along a plane of cleavage which is usually found without difficulty. A surprisingly smooth surface is left. The opening in the vessel is then sutured. This method has a place in removing very short areas of clot from large arteries such as the iliac in which there is a wide lumen and a vigorous stream to discourage thrombosis. The operation is not applicable to arteries of narrower calibre in which, as might be expected, clotting recurs.

Special Investigations

The state of the peripheral circulation may be studied in several different ways. Venous occlusion plethysmography enables the actual flow of blood in the limb to be measured quantitatively, and is therefore particularly valuable. Skin temperature, and other tests, measure the flow qualitatively. These studies are valuable in research, and in the more unusual and difficult cases of arterial obliteration, but for routine work a careful clinical examination is quite adequate. Arteriography is an exception to this rule. It is essential if arterial grafting is to be considered, as the exact extent of the clot, and the state of the arterial tree, must be known. Percutaneous puncture allows repeated examinations, and is usually done at the level of the common femoral artery. When it is suspected, because of absence of the femoral pulses or because of pain in the buttocks or thighs on walking, that the iliac vessels may be involved the blocked areas must be visualized by injection at a higher level. This can be done by means of translumbar aortography.

Paravertebral sympathetic block has been tried as a test to predict the effect of sympathectomy, but its effect upon claudication has not been found to correspond at all closely with that of operation. It has therefore little place as a pre-operative test in patients with claudication, but is sometimes useful in patients with ischaemia of the skin.

Next Refresher Course Article.—"Myxoedema," by Dr. A. W. Spence.

BRITISH EMPIRE LEPROSY RELIEF ASSOCIATION

The annual meeting of the British Empire Leprosy Relief Association, which was held in London on May 21, was to have been addressed by the Rt. Hon. Oliver Lyttelton, but his absence in Kenya prevented his attendance. In his place an address was given by the Rev. P. T. B. CLAYTON, founder of Toc H. Mr. Clayton said that a new era of hope had dawned with the sulphone treatment of leprosy, but, although the increase in services and child adoptions had been considerable, the areas where treatment was available to the majority of sufferers were still few, and elsewhere only one sufferer in thirty, and until recently often only one in a hundred, were within reach of cure. In Nigeria, leprosy control had been gained by establishing clinics and segregation villages around a central leprosarium, even before Dr. John Lowe's experiments at the association's research unit with volunteer patients had brought still more effective relief. The child adoption scheme had also contributed to the wane of the disease in parts of Nigeria. The demand was for fresh centres in the more remote hotbeds of infection. Although new homes were being built, they existed only in tens where hundreds were wanted, and little advance had as yet been made towards the establishment of the East Africa Research Centre. Thanks to the work of voluntary helpers, said Mr. Clayton, and the increasing aid from firms and trade unions, the receipts of the association had risen from £11,450 in 1939 to £69,876 in 1952.

Sir LEONARD ROGERS, surveying twenty years of investigation and treatment of the disease, spoke of the difficulties which arose when fear of segregation drove victims to hide the disease until it was far advanced, so that doctors could not find early cases to treat. In the Nigerian

Eastern Provinces, the most heavily infected area, the incidence of the disease was estimated as being twenty times greater than in India.

Need for a Research Unit in East Africa

Dr. R. G. COCHRANE, medical secretary of the association, in his report, described his visit last autumn to East and Central Africa and to Nigeria, where the system of village colonies combined with large-scale out-patient work had been shown to be most suited to African conditions. Within the next decade the Eastern Provinces were likely to demonstrate complete control of the disease in that region. Dr. Cochrane paid a tribute to Sir Leonard Rogers, "architect and planner" of the association, to whom, and to whose successor, Dr. Ernest Muir, so much of the achievement was due. Thanks to Dr. Paul Brand at Vellore, South India, a new constructive approach had been made to the residual deformities of leprosy. The possibility of yet another effective line of attack was to be found in the recent attempt to increase resistance, particularly in children, by the use of B.C.G. Nevertheless, Dr. Cochrane added, any optimism about the control of leprosy must always be tempered with great caution; even the sulphone remedies had their drawbacks. The process of bacteriological cure was painfully slow, and there was difficulty in getting advanced cases to the stage at which they could tolerate an effective therapeutic dose of the drug. Many persons were found to be infective after years of treatment. For these reasons still more knowledge of the disease was needed, and there was call for further support to make the planned "Belra" Research Unit in East Africa an actual fact.

MEDICAL CORONATION HONOURS

The names of the following members of the medical profession were included in a Coronation Honours List published in *Supplements* to the *London Gazette* on June 1:

K.C.M.G.

Sir JAMES BENNETT HANCE, K.C.I.E., O.B.E., M.D., F.R.C.S.Ed. Lieutenant-General, I.M.S. (retired). Medical Adviser and President, Medical Board, Commonwealth Relations Office.

K.B.E. (Military Division)

JAMES MACCONNELL KILPATRICK, C.B., O.B.E., M.B., B.Ch., D.P.H. Acting Air Marshal, Royal Air Force. Honorary Physician to the Queen.

K.B.E. (Civil Division)

FRANCIS GORDON BELL, *M.C.*, M.D., F.R.C.S., F.R.C.S.Ed. Formerly Professor of Surgery in the University of Otago, New Zealand.

Knighthood

The Hon. Mr. NICHOLAS ATTYGALLE, F.R.C.S., F.R.C.O.G. President of the Senate, Ceylon. For services to medicine.

DAVID CAMPBELL, *M.C.*, M.D., F.R.F.P.S. President of the General Medical Council and Regius Professor of Materia Medica and Therapeutics in the University of Aberdeen.

FRANCIS MARTIN ROUSE WALSHE, O.B.E., M.D., D.Sc., F.R.C.P., F.R.S. President of the Royal Society of Medicine. Consulting Physician to University College Hospital, London.

C.B. (Military Division)

JOSEPH CLINTON COLLINS, C.B.E., M.R.C.S., L.R.C.P. Major-General, late R.A.M.C. Honorary Surgeon to the Queen.

FREDERICK KNOWLES ESCRITT, O.B.E., M.R.C.S., L.R.C.P. Major-General, late R.A.M.C. Honorary Surgeon to the Queen.

C.M.G.

PHILIP STANLEY FOSTER, M.B., Ch.B., F.R.C.S., F.R.A.C.S. Consulting Surgeon, Christchurch Hospital. Chairman, New Zealand Medical Council.

GEORGE MACDONALD, M.D., M.R.C.P., D.P.H., D.T.M. Professor of Tropical Hygiene in the University of London and Director of the Ross Institute of Tropical Hygiene.

C.V.O.

JOHN NIGEL LORING, M.R.C.S., L.R.C.P. Apothecary to the Household of H.M. the Queen.

C.B.E. (Military Division)

KENNETH BARRON FRASER, E.D., M.S., F.R.A.C.S. Colonel, Royal Australian Army Medical Corps.

PATRICK BRUNTON LEE POTTER, O.B.E., M.D., D.P.H., D.T.M.&H. Air Commodore, Royal Air Force.

FREDERICK ELVY LIPSCOMB, M.R.C.S., L.R.C.P., D.P.H., D.T.M.&H. Air Commodore, Royal Air Force. Honorary Physician to the Queen.

SAMUEL GERALD WELDON, M.B., B.Ch., D.P.H. Surgeon Captain, Royal Navy.

FREDERICK WILLIAM WHITEMAN, O.B.E., M.B., Ch.B. Colonel (temporary) Pakistan Armed Forces Medical Services.

C.B.E. (Civil Division)

WILLIAM GEORGE BARNARD, F.R.C.P. Dean of St. Thomas's Hospital Medical School and Director of Pathology at St. Thomas's Hospital. Professor of Pathology in the University of London.

GILBERT BROWN, M.B., Ch.B., F.F.A.R.C.S., D.A., of Adelaide, South Australia. For services in the development of anaesthetics.

THOMAS MORRIS DAVIES, M.R.C.S., L.R.C.P. Deputy Director-General of Medical Services, Ministry of Pensions.

ALAN TAYLOR HOWELL, M.B., B.Chir., D.T.M. Director of Medical Services, Tanganyika, Colonial Medical Service.

WILLIAM LESLIE, *M.C.*, T.D., M.B., B.S. J.P. for the Borough of Penzance. For political and public services in Cornwall.

ARCHIBALD DANIEL MARSTON, F.R.C.S., D.A., F.F.A.R.C.S. Lately Dean of the Faculty of Anaesthetics, Royal College of Surgeons of England.

ARNOLD ASHLEY MILES, M.D., F.R.C.P. Director, Lister Institute of Preventive Medicine, London.

GILBERT INNES STRACHAN, M.D., F.R.C.P., F.R.C.S., F.R.C.S.Ed., F.R.C.O.G. For political and public services and for services as Professor of Obstetrics and Gynaecology in the University of Wales.

RICHARD ROBERTSON TRAIL, *M.C.*, M.D., F.R.C.P. Medical Director, Papworth and Enham-Alamein Village Settlements for the Tuberculous.

M.V.O. (Fourth Class)

JAMES LAWRENCE BUNTING ANSELL, M.R.C.S., L.R.C.P. Surgeon Apothecary to the Household of H.M. the Queen at Sandringham.

O.B.E. (Military Division)

JOHN MANSEL REESE, M.R.C.S., L.R.C.P., D.P.H. Surgeon Commander, Royal Navy.

O.B.E. (Civil Division)

FRANCIS WARD ALLINSON, M.B., B.S., F.R.C.S. Professor of Surgery, Medical College Hospital, Dacca, Pakistan.

CHARLES ANTHONY BOUCHER, D.M., D.P.H. Medical Officer, Ministry of Health.

CECIL BURNHAM, M.B., Ch.B., F.R.C.S.Ed. Lately Commandant, Star and Garter Home for Disabled Soldiers, Sailors, and Airmen, Richmond, Surrey.

WILLIAM JOHN HUGHES BUTTERFIELD, M.D., M.R.C.P. Member of the Scientific Staff, Medical Research Council.

RICHARD ALEXANDER SEYMOUR CORY, M.B., Ch.B. Senior Medical Officer, Colonial Medical Service, Tuberculosis Sanatorium, Jamaica.

KENNETH JOHN GRANT, M.B., Ch.B., D.P.H. Medical Officer of Health, Great Yarmouth. For services during the recent floods in the Eastern Counties.

EBEN STUART BURT HAMILTON, *M.C.*, M.B., Ch.B., F.R.C.S.Ed. Commissioner, Duke of Lancaster's District, St. John Ambulance Brigade.

ALBERT JOSEPH HAWE, M.D., F.R.C.P., D.T.M.&H. Senior Specialist, Colonial Medical Service, Gold Coast.

GORDON KING, F.R.C.S., F.R.C.O.G. Professor of Obstetrics and Gynaecology in the University of Hong Kong.

JAMES SANDERSON MCGREGOR, M.D., D.P.M. Medical Superintendent, Saxondale Mental Hospital, Radcliffe-on-Trent, Nottinghamshire.

WILLIAM JOSEPH MOODY, M.B., B.Chir., F.R.C.S.Ed. Lately Medical Adviser to the British Political Resident and Chief Quarantine Medical Officer, Persian Gulf. Lieutenant-Colonel, I.M.S. (retired).

GEORGE RANKINE, *M.C.*, M.B., Ch.B. General Practitioner, Dundee.

SARAH ANDERSON JAMIESON RANKINE, M.B., Ch.B. Medical Officer in charge of St. Margaret's Hospital, Poona, Bombay.

HENRY RICHARDS, M.B., B.S., D.P.H., D.T.M.&H. Assistant Director (Public Health), Sudan Government.

GEORGE ROBERTSON ROSS, Ph.D., M.B., Ch.B., D.P.H. Member of the Public Services Board, Southern Rhodesia.

EMRYS CADWALADR THOMAS, L.R.C.P.&S.Ed. Director of the Victoria Hospital, Damascus.

JOHN DUNCAN WHITE, M.B., Ch.B., D.M.R.E. Director, Radiodiagnostic Department, Hammersmith Hospital.

THOMAS MACFARLANE WILKS, M.B.E., T.D., M.R.C.S., L.R.C.P. Area Commissioner, St. John Ambulance Brigade, London. For services during the recent floods in the Eastern Counties.

DONALD BAGSTER WILSON, M.D. Director, East Africa Malaria Unit, Colonial Medical Service.

M.B.E. (Military Division)

JOHN WILLIS COOMBE. Lieutenant, Royal Australian Army Medical Corps.

M.B.E. (Civil Division)

HENRY SIDNEY ATKINSON, B.M., B.Ch. Chairman of Committee, No. 135 (Reigate and Redhill) Squadron, Air Training Corps.

DOROTHY DELBRIDGE, M.B., Ch.B., D.T.M. For medical services in Fiji.

FRANCIS JOHN GRAHAM, L.R.C.P.&S.I. For services to the community in New South Wales.

GEOFFREY BUCKLAND ORBELL, M.B., Ch.B., of Invercargill, New Zealand. For scientific work.

WILLIAM OLIVER PETRIE, M.B., Ch.B.Ed., D.T.M.&H. Medical Officer, Nyasaland, Colonial Medical Service.

RONALD REES POWELL, M.R.C.S., L.R.C.P. Chairman, Reigate Unit Committee and Southern Area Representative, Sea Cadet Council.

SOO HOY MUN, M.B. Honorary Medical Officer, Chinese Maternity Hospital, Federation of Malaya.

The Coronation Honours List includes also the appointment to the Order of the Companions of Honour of the Right Hon. Thomas Johnston, P.C., Hon.F.R.C.S.Ed., Secretary of State for Scotland from 1941 to 1945; Knighthoods for Alderman J. W. Bowen, C.B.E., chairman of the North-east Metropolitan Regional Hospital Board and the National Health Service General Whitley Council, Mr. H. N. Linstead, O.B.E., M.P., secretary of the Pharmaceutical Society, and Mr. Frederick Messer, C.B.E., M.P., chairman of the Central Health Services Council and lately chairman of the North-west Metropolitan Regional Hospital Board; and the C.B.E. for Mr. W. G. Senior, O.B.E., principal dental officer at the Ministry of Health.

MEDICINE UNDER THREE QUEENS

EXHIBITION AT THE WELLCOME MUSEUM

As part of its Coronation celebrations the Wellcome Historical Medical Museum has prepared an exhibition illustrating "Medicine Under Three Queens: Elizabeth I, Anne, and Victoria." The exhibition was formally opened at 28, Portman Square, London, W.1, by Sir Zachary Cope on June 5. In introducing Sir Zachary, Dr. E. Ashworth Underwood, director of the Museum, explained that the three periods had been chosen because they brought out the characteristics of the British people: these characteristics were well shown by the medical men of the times.

Sir Zachary Cope, who gave a short address on "The Birth of Modern Medicine," paid a tribute to the trustees of the Wellcome Foundation for their maintenance of a museum and library invaluable to medical historians. He said that his theme was most appropriately illustrated by the progress of medicine during these three reigns. Progress was brought about by the effect of an idea on a fact. Up to the time of Elizabeth I no physician had acted upon this axiom, and true progress had been impossible. During her reign modern anatomy and physiology had had their beginnings, the *De Fabrica* of Vesalius had been translated into English, and the first steps taken towards the conception of modern medicine. Harvey had been born, and his ideas on circulation had been formulated during this reign. English was being used considerably for the first time. During the next century little progress was made, and the quickening of modern medicine was left until the time of Anne. It was during her reign that Cheselden saw the need for the systematic teaching of anatomy. In 1711 he published a syllabus and gave lectures on the subject, and, with Hauksbee, on physics as related to the human body. There followed the foundation of more hospitals and medical schools. The Apothecaries Act of 1815 must be regarded as only a pseudo-gestation. The real birth of modern medicine occurred in 1858 with the passing of the Medical Act and the formation of the General Medical Council. In the same year Virchow had published his *Cellularpathologie* and Pasteur was completing his work on fermentation. A year later appeared Florence Nightingale's *Notes on Nursing*, and it could be said that nursing was born within a year of modern medicine. From the birth of Harvey to 1858 was a period of 280 years; the period of human gestation was 280 days. The last hundred years had covered the childhood, development, and adolescence of modern medicine, and to-day its position was greater and more powerful for good than it had ever been in any era of history. Sir Zachary wished that the reign of Elizabeth II had been included in the exhibition, for he felt that the present was a great moment in medicine. Revolutionary discoveries were on the way, and the fact that older members of the profession were often unable to understand papers now being published in the journals showed that something great might be pending.

A vote of thanks to Sir Zachary Cope was proposed by Sir Gordon Gordon-Taylor, and seconded by Sir Allen Daley. The exhibition, which includes books, portraits, instruments, etc., illustrating outstanding medical men and their achievements during the three reigns, will remain open until further notice.

CLIMBING EVEREST

SOME NOTES ON THE MEDICAL TEAM

The doctor in medical charge of the Everest expedition is Dr. Michael Ward. At the age of 12 he climbed the Matterhorn, and as a medical student at Cambridge he clambered round the roofs with its famous night climbers. In 1951 he went to the Himalayas with Shipton on the reconnaissance expedition which led to the present successful approach to the summit. He was the first then to see the footprint of the Abominable Snowman. Dr. Ward's main concern now is looking after the medical care of the party, and this duty has come first when it was thought he might be one of the men to reach the summit.

Dr. L. G. C. Pugh, a physiologist from the Medical Research Council, is not a climber, but accompanied the party in order to carry out tests on the physiological effects of high altitude. He accompanied Shipton's last expedition and was mainly concerned with the use of oxygen. Should it be given as a cocktail when deterioration is setting in, or should it be used all the time above certain heights, even when sleeping in one's tent? In this debate he has always been a firm supporter of the latter method. His duty has been to remain in the region of the base camp and perform physiological tests on climbers coming down from higher altitudes.

Mr. R. C. Evans, a surgeon in Liverpool, is regarded as one of the best climbers in this country, and has all the qualities of what experienced climbers call a "good executive technical mountaineer." A short, quiet, unobtrusive man, he learned his climbing in the Welsh mountains, and climbed in the Himalayas in 1950 and 1952. Strongly

fancied as one of the men most likely to reach the summit, he was selected with T. D. Bourdillon for the first attempt on it with a closed oxygen apparatus, but they failed to reach it.

Perhaps the most trying task has fallen to Dr. Ward. The medical problems appear the whole way from Khatmandu to the summit and back. In the swamps and jungles there are bites and stings and leeches, and a fair chance of contracting malaria. Proguanil was given to each man, and sulphaguanidine was part of the diet right up to the glacier, where water can be obtained from melted snow. On the way up Dr. Ward watched the acclimatization of the party and later deterioration, and took apparatus for testing the climbers at various levels. First and foremost came the job of caring for the health of the party. High on the mountainside sore throats and tonsillitis are a constant trouble —probably due to panting from oxygen-lack in an atmosphere of low humidity which can reach −20° C. Breathing apparatus used on previous expeditions failed in its purpose but cut down sore throats through retaining humidity. Carelessness can quickly lead to frostbite and snow blindness. A doctor on a previous expedition lost a finger-tip through pressing a camera-shutter with an ungloved hand.

For all the excitement in the Press, a good deal of the climbers' time has been spent in loneliness and monotony. They took books with them, and, according to Ward, their way of thinking and taste in reading changed greatly on Everest. Thought is mainly devoted to matters of food—hot meals being impossible when boiling water is only lukewarm. Over 17,000 feet one ceases to think of the opposite sex, he claims, and men who rarely read anything but crime stories crave for the classics. Dr. Ward took Jane Austen and the Brontës with him in order to defeat monotony, "because I have never been able to read them down here. On the last expedition we all read Trollope and enjoyed him, yet none of us had ever been able to read him before. It was because he gave such a vivid picture of the exciting everyday things."

CORMAC SWAN.

Nova et Vetera

A VANISHED CULTURE

Uttermost Part of the Earth. By E. Lucas Bridges. (Pp. 558; illustrated. £1 10s.) London: Hodder and Stoughton. 1951.

This unique book is the only one by its author. It appeared in his old age, shortly before his death, and took its place as a classic from the day of publication. Bridges was the last, and probably the first, educated Englishman who was born and reared among savages of a Stone Age culture. He acquired their language almost as early as his own, had an interest in their ways of life and thought, and travelled and lived with them for many of his adult years. He was a member of a family who, in their own ways, both boys and girls, were as intelligent and adventurous as himself. The book is long, but any one of the 48 chapters may be read separately, for each is a stirring tale of adventure. I know no better book for older boys and girls who love adventure, but it is also of great scientific interest. Medically it tells much of the powers of endurance of different races when long exposed to the most rigorous climatic conditions. It also tells of the reactions of different races to various medical and surgical conditions. Anthropologically it is not only by far the best record of a people now extinct but, above all, probably the only record of life among savages in terms of individual personalities. It displays the infinite variety of human character to be found no less among primitive peoples than among ourselves.

The "Uttermost Part of the Earth" is the irregular group of great islands known as Tierra del Fuego in the extreme south of South America and is the nearest to Antarctica of any permanently inhabited land. It is impossible to describe in a short space the pulse-stirring character of this book, and I shall confine myself to a few words first about the author's father—who is perhaps the real hero of the story—and then about the people among whom his life was passed.

Starting a Settlement

Thomas Bridges, father of the author, was adopted in childhood by a clergyman interested in missionary work among the Fuegians. Several missionary attempts had been made, but with considerable loss of life. At last it was suggested that a missionary base might be formed in the Falklands, and Keppel Island was given by the Government for the purpose. The clergyman with his wife and family, including Thomas Bridges still in his early teens, embarked in 1854 for Keppel in a schooner of 88 tons register. During the next years, with great difficulty and after repeated attempts, they persuaded a few Fuegians to settle in Keppel. These learned a few words of English and the missionary group learned a little of one of the native languages, but Thomas, still a stripling, applied himself to this task with special energy and skill. After some years it was decided to make another attempt to form a settlement on Tierra del Fuego. With a single exception the entire crew and the missionary party were murdered by the natives. After consideration the remaining missionaries on Keppel decided that the project was hopeless and returned to England. Thomas Bridges, now 18 but the only living expert in a Fuegian language, elected to remain and was left in charge of the settlement. He perfected his knowledge of the language and prepared in manuscript a dictionary and grammar of it which now, after many many adventures of their own —*habent sua fata libelli*—rest among the treasures at the British Museum.

Stone Age

He then made the voyage to Tierra del Fuego, where the natives were astonished to be addressed by a white man in their own tongue. By 1867 he had succeeded in establishing a small farm worked by a few natives on one of the outlying islands. Much of the best story-telling in the book is the life of this most gallant, able, and determined man. He returned to England, where he persuaded a lady to marry him and to go with him to Tierra del Fuego. They had three sons and three daughters, the remarkable lives of all of whom are indicated here. This splendid man died in 1898, apparently from haemorrhage from ulcer of the stomach, at a post that he had established in the land of his choice. He was about 57.

As to the people that he served: despite the severity of the climate and the tempests with which their land is swept winter and summer, they were normally naked, using mantles of skins only for special occasions. They were ignorant of metals, had no domestic animals, and did not cultivate the earth. They lived mainly on wild llamas that they were able to kill with their bows and stone-tipped arrows, combined with a few birds, plants, and fish that they gathered. The women fished and they alone could swim. The men seem normally to have had two wives. As between tribe and tribe they were very ferocious, making nothing of the life of one who could not speak their language, but they cared for their old people. They were not cannibals. Neither the author of this book nor his father was able to find a trace of anything that could be called a religion. They were expert in making their weapons, notably their complex bows and harpoons, on which they chiefly relied for their food.

The name of their country, "Land of Fire," seems to be due to the custom of small parties signalling to each other by lighting fires. They had no fixed settlements. An epidemic of measles that affected all the Bridges family led to the death of great numbers of the Fuegians. They were later practically exterminated by tuberculosis, syphilis, and alcohol. Hardly a memory of them can now survive, which makes this remarkable book at once a memorial of a people, of a language, of a family, and of a man.

CHARLES SINGER.

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

Misuse of Drugs in Tuberculosis

SIR,—May I make a plea for the more thoughtful use of the new drugs in the treatment of tuberculosis? It is a not uncommon experience at this hospital to receive patients from general hospitals who have already received a very large dosage of streptomycin, amounting in one case to over 170 g. Although great improvement in these cases may have occurred, it is achieved almost inevitably at the cost of the development of resistance to the drug, even though it may have been given in combination, and risks of permanent damage to the eighth nerve at this dosage cannot be negligible. I do not need to stress the disadvantages of the development of resistance, which are well known, except to mention that patients received here in this condition for whom major surgery is contemplated are, as a result, rendered hazardous subjects, particularly if resection is envisaged.

There has always been a proper strategy in the treatment of tuberculosis, which must essentially be unhurried, and it is important to integrate these new and effective agents with it. I would suggest that, except in a very acute or miliary case, in the present state of our knowledge, streptomycin should be given in 1-g. doses on alternate days or even every third day, combined with a total daily dosage of 12–15 g. P.A.S. and/or 200 mg. of isoniazid, until 30 g. of streptomycin has been given; radiological improvement will usually continue for some weeks after the end of such a course, and the patient can then be reassessed. He is unlikely to have developed resistance to any of these drugs, and they can be similarly given again in further courses either to secure more improvement, to cover major surgery, or to treat relapses occurring at a later date. It may also prove that the middle-aged "chronic" who is unsuitable for collapse therapy may be kept reasonably fit and rendered temporarily non-infectious by similar periodic courses, provided resistance has not been allowed to develop by maldosage.

Greatly improved results are possible in the treatment of tuberculosis following the introduction of these new drugs, and it is essential, therefore, to use them to the best advantage.—I am, etc.,

London, N.W.9. W. E. SNELL.

Anticoagulants in Myocardial Infarction

SIR,—I thought that the questions raised by Mr. John Fry (*Journal*, May 16, p. 1109) and further elaborated by Dr. R. A. Murray Scott and Dr. John C. Ryle (*Journal*, May 30, p. 1223) had been adequately answered in the joint paper and correspondence with Dr. K. Shirley Smith.[1 2] The conclusions reached in a series of 200 cases of cardiac infarction collected from general, consultant, and hospital practice agree with Mr. John Fry's statement that the incidence of severity of the disease is about equal in general and hospital practice. We were also able to show that the mortality figures in untreated cases of slight and moderate cardiac infarction (that is, in patients *without* intractable pain, severe shock, cardiac enlargement, gallop rhythm, and heart failure) for the first two months following infarction were only 2%. These patients made up more than half of the whole series; this means that anticoagulant treatment may not be required in half of the cases. The assessment of treatment is done on clinical grounds and is in the province of any experienced general practitioner. The objection that a slight cardiac infarction may complicate into a severe one is valid, although this is an uncommon event; the patient then has recurrent angina following the bout of infarction pain, and this in itself is an indication for anticoagulant treatment.

Ethyl biscoumacetate ("tromexan") was a distinct advance over dicoumarol, and so is phenylindanedione ("dindevan") over ethyl biscoumacetate.[3] However, all require laboratory control, although phenylindanedione less often. If the patient is reliable enough to report discoloration of the urine or lumbar pain—haematuria is by far the most frequent haemorrhagic manifestation—anticoagulant treatment can be safely carried out at home if twice-weekly prothrombin estimation is practicable during the first fortnight and once weekly later.

I agree with Dr. Murray Scott that shock following cardiac infarction needs energetic treatment; I am not sure if leptazol-ephedrine injections will always be effective. The danger of persistent shock is so great that it far outweighs the danger of removal to hospital where only it can be effectively treated with intravenous infusions and pressor drugs.—I am, etc.,

London, N.W.3. C. PAPP.

REFERENCES

1 *British Medical Journal*, 1951, 1, 1471.
2 Ibid., 1952, 2, 515.
3 Ibid., 1953, 1, 650.

SIR,—Mr. John Fry in his letter on anticoagulant therapy (*Journal*, May 16, p. 1109) raises several interesting problems, to some of which there would appear to be no easy answer.

The results in all large series of treated and control cases of coronary thrombosis so far published in this country and America agree on the value of anticoagulants in reducing the mortality and morbidity of this disease. Therefore, would it not appear to be our duty to use these drugs in all cases wherever possible? I. S. Wright[1] has argued against those who would only treat the severe cases in this way by pointing to the fact that the minor attack may be the herald of the major catastrophe.

In the decision as to which cases are in urgent need of anticoagulants the laboratory may be able to provide some help. Rosenthal,[2] using a simplification of the Waugh and Ruddick heparin tolerance test,[3] found that in 14 cases out of 19 of recent coronary thrombosis a result below the normal range was obtained (i.e., clotting was accelerated). At Withington Hospital we have been using a simple heparin retarded plasma clotting test for some time. In 37 of 50 cases of recent thrombo-embolic disease clotting was found to be "accelerated" at the initial test. Heparin in addition to dicoumarol has been immediately administered in such cases. This type of test may also be of value in determining when anticoagulant therapy may be safely discontinued.—I am, etc.,

Manchester. L. POLLER.

REFERENCES

1 *Circulation*, 1952, 5, 161.
2 Ibid., 1952, 6, 257.
3 *Canad. med. Ass. J.*, 1944, 51, 11.

Poliomyelitis in Copenhagen

SIR,—In December, 1952, I was privileged to visit the hospital in Copenhagen where the poliomyelitis cases were treated. It appears, from articles in the *Journal* of May 30 (pp. 1208 and 1216), that Professor Lassen has, unwittingly, given the impression that he was responsible for the introduction of a new method of treatment of cases with respiratory paralysis. I am sure he would wish this to be corrected.

When, last summer, 27 of the first 31 of these cases had died under the methods of treatment orthodox in Europe, Dr. Bjørn Ibsen, then chief anaesthetist at the neighbouring university hospital, attended a conference called by Professor Lassen. Dr. Ibsen's everyday experience of the artificial control of respiration and his knowledge of the American literature enabled him to suggest certain radical improvements. When, eventually, his suggestions were accepted, he and his anaesthetist colleagues from the other Copenhagen hospitals took over this aspect of the treatment of these cases and provided continuous supervision through the months of the emergency. Early tracheotomy has previ-

ously been advocated for the proper control of pharyngeal secretions; the use of a cuffed tracheal tube and of artificial respiration by manual compression of a bag (techniques employed daily by anaesthetists, but unfamiliar to epidemiologists) with a high rate of gas-flow and a to-and-fro carbon dioxide absorber (not "closed circuit") were introduced and adapted to the demands of this emergency by Ibsen and his colleagues. They also trained and supervised the large number of medical students employed by Professor Lassen. As the method they used is likely to be developed further, it would be better left unnamed; if a name is to be attached, it must be that of Ibsen.—I am, etc.,

London, S.W.1. GEOFFREY ORGANE.

Acute Malaria Probably Precipitated by A.C.T.H.

SIR,—When about eighteen months ago I started the studies on the action of A.C.T.H. and cortisone in the complications of leprosy already recorded in the *Journal* of October 4, 1952 (p. 746), a correspondent informed me that it had been recorded that these hormones could precipitate an attack of malaria in a person harbouring a latent infection. In this area, malaria (*P. falciparum*) is highly endemic and many persons have latent infections. I have used A.C.T.H. and cortisone in many Africans, mainly adults, and, although a few of these patients have had malaria in the following days, I have seen no reason to ascribe these attacks to the hormone treatment. Recently, however, I have had occasion to give A.C.T.H. to a European who was taking pyrimethamine ("daraprim") as a malaria suppressant, and the hormone apparently provoked a fulminating attack of malaria. The details are here summarized.

A European woman, long resident in the Tropics, with a history of two attacks of malaria long ago, came to Nigeria in December, 1952, and had been taking pyrimethamine, one tablet once a week, as a malaria suppressant, with the complete absence of any signs of malaria. In April, 1953, she developed extensive inflammation and irritation of the skin, which here is frequently associated with filarial infection. Blood examination revealed no microfilaria, but eosinophils formed 38% of the white cells present. Local skin treatment brought no relief, and the condition was so distressing that a course of diethylcarbamazine ("hetrazan") was started. Within 48 hours there was, as usual, an intense exacerbation of the skin symptoms, which fact tends to support the diagnosis of filarial infection as the cause. Antihistamines gave little relief, so an injection of 50 mg. of A.C.T.H. was given, with immediate relief of symptoms. Diethylcarbamazine was continued, and three days later the dermatitis was markedly improved. Then, while diethylcarbamazine was still being given, there occurred a fulminating attack of malaria caused by *Plasmodium falciparum*; in addition to very high fever, there was intense purging and great weakness, and for 24 hours the patient's condition was critical. With prompt diagnosis and energetic treatment (quinine by injection, and chloroquine) the fever was controlled, and the patient is now convalescent. Some diarrhoea with mucus and many red blood cells in the stool has persisted for several days. Repeated examination for *Entamoeba histolytica* has given negative results; the diarrhoea has been completely uninfluenced by phthalylsulphathiazole. There is clear evidence of ulceration of the colon with slow healing. I am of the opinion that the bowel condition was caused by the malaria; profuse diarrhoea is a frequent manifestation of malarial infection here, particularly in children and non-immunes. In the present case the clinical picture from the onset of the fever was that of "choleraic malaria."

It is realized that it is unwise to argue from one case. This present case, however, was striking. A woman was, like many others, taking pyrimethamine for suppressing malaria, with very satisfactory results; she received one injection of A.C.T.H., and on the same day actually took, in my presence, a tablet of pyrimethamine. Three days later there was a fulminating malaria, with very severe intestinal symptoms, such as is seen only in non-immunes who are taking no suppressive treatment whatever. The evidence that the A.C.T.H. precipitated the malaria is, I feel, strong; moreover, the intestinal symptoms, if not due to malaria, could be due to the acute exacerbation by A.C.T.H. of a latent bowel infection. These ideas are in keeping with knowledge of the action of A.C.T.H., which can much reduce the tissue cell activity which is keeping an infection in check. So far, little A.C.T.H. or cortisone has been used in the Tropics; this is possibly the reason why incidents such as the present one have not been common.

This case indicates (*a*) that A.C.T.H. can give striking relief in the severe allergic reactions often seen in cases of filariasis being treated with hetrazan; (*b*) that it seems probable that A.C.T.H. can temporarily neutralize immunity to malaria (and possibly other infections) and provoke a fulminating attacks in persons in whom such infections are latent; and (*c*) that therefore A.C.T.H. cannot be used with safety in such cases. It seems, however, possible that such dangers of giving A.C.T.H. can be overcome by the simultaneous use of energetic measures to combat such infections. If A.C.T.H. and cortisone are to be used in malarious countries, or in persons returning from malarious countries, this matter should receive consideration. Further studies of this matter are needed.—I am, etc.,

Uzuakoli, E. Nigeria. JOHN LOWE.

Relief of Pain in Childbirth

SIR,—The letter of Mr. Ian Simpson (*Journal*, May 16, p. 1110) reminds us of Sir James Young Simpson's valiant attempt to help the woman in labour, and it is indeed fitting that just one hundred years after Queen Victoria received the benefits of analgesia, we should look more closely into the position of analgesia in labour to-day.

Recent correspondence in *Public Health*[1] and the *Medical Officer*[2 3] and the address of the late F. Neon Reynolds to the British Medical Association in Dublin, 1952, have shown that this position is far from satisfactory. I have received a number of letters from mothers in various parts of England, all telling a sad and sorry tale. One describes how she was given gas and air for her last pain only. This practice is not uncommon, and one cannot escape the conclusion that the gas-and-air machine is sometimes used as a face-saving device, as the patient who receives gas for only one pain goes down in the records as having received analgesia.

Another mother tells me that she did not get gas and air because the machine was empty. So the melancholy record goes on. It is perfectly clear to any honest and sincere observer that our girls are not receiving the attention which is their due. This, twenty years after the introduction of gas–air analgesia. Some hospitals have shown how great can be the benefits of modern analgesia to the woman in labour, and in domiciliary midwifery the County Medical Officer of Health for Hertfordshire has conclusively demonstrated what wonderful results can be obtained from his own inspiring leadership in this county. Taking England as a whole, the relief of pain in maternity falls lamentably short of what might reasonably be expected, and the help given under nationalized medicine compares very unfavourably, both in hospital and domiciliary midwifery, with that provided by the Hertfordshire County Council.

Let there be no misunderstanding. Whether we use chloroform or nitrous oxide or trichlorethylene, or any other thing, no satisfactory results can be expected until there is a genuine and sincere desire to provide relief from pain and unless the necessary organization for such a service is forthcoming.—I am, etc.,

New Barnet. J. E. ELAM.

REFERENCES

1 *Publ. Hlth (Lond.)*, 1953, **66**, 79.
2 *Med. Offr*, 1953, **89**, 75.
3 Ibid., 1953, **89**, 97.

Haemophilia with Respiratory Obstruction

SIR,—The paper by Dr. A. C. Macdonald and his colleagues (*Journal*, May 23, p. 1144) recalls a similar case in which I was involved about a year ago.

The patient was a healthy young man of 24, who was well known by his doctor and dentist to be a "bleeder." He had attended the local dental hospital for toothache and it was decided to fill the cavity in the tooth under a local anaesthetic inferior dental nerve block. Unfortunately the needle used for the injection transfixed the inferior dental vessels and rapid extravasation of blood developed in the soft tissues of the left cheek. The swelling developed so rapidly that the dental filling had to be abandoned. He was admitted to hospital 12 hours

later with difficulty in swallowing due to gross extravasation of blood in the tissues of the left cheek and the floor of the mouth. The tongue was purple in colour, oedematous and filled almost the whole of the oral cavity. There was no actual bleeding into the mouth, and the condition seemed to be entirely one of extravasation into the soft tissues.

During the next 12 hours the swelling increased steadily. The tongue not only filled the oral cavity, but protruded from the mouth. There was a large swelling in the left side of the neck, which appeared to be fluctuant in places. By this time difficulty in breathing was obvious and increased rapidly. Surgical treatment became imperative. As in the case quoted by Dr. Macdonald, it was decided to explore the swelling in the neck. To our dismay, no localized collection of blood was found, only a diffuse interstitial extravasation of blood in the tissues of the neck and the floor of the mouth. To provide an airway, a formal tracheotomy was performed. It was considered unwise by our anaesthetic colleagues to attempt tracheal intubation through the nose. The patient's recovery was complicated by persistent oozing from both wounds. The wound on the left side of the neck broke down, and even after packing with fibrin foam soaked in thrombin solution and closing the wound by suture, the oozing still continued for several days. It took some 10 weeks for the swelling of the face and tongue to subside and the wounds of the neck to heal soundly. In all, the patient was given 24 pints (13.6 l.) of blood in the course of one week. Nine pints (5.1 l.) of this blood was fresh, taken on the spot from volunteer donors and transfused almost immediately.

It is generally recognized that transfusion of even one pint (0.568 l.) of fresh blood will diminish materially even severe bleeding from a haemophilic patient. In our case it was alarming to find that transfusion of large amounts of fresh blood did not have this dramatic effect. Two factors may have contributed to this. Although we had asked specifically for fresh blood, not more than 24 hours old, some of the blood sent to us as "fresh" from the Regional Blood Transfusion Service was found to be over 48 hours old. The transfusion of large amounts of stored blood over a short period must necessarily increase the concentration of citrate in the circulating blood. This might affect the normal blood-clotting mechanism in a patient who has already lost a large amount of blood. Those of us who have assisted at emergency gastrectomies for persistent haematemesis have often remarked upon the unusual amount of bleeding which occurs during the operation. Since all these patients have had large amounts of blood transfused both before and during the operation, overdosage with citrate is a possible explanation. I am not aware, however, that any proof has been adduced to support this clinical impression.—I am, etc.,

Salisbury. MICHAEL N. TEMPEST.

Treatment of Ringworm of the Scalp

SIR,—Dr. B. A. Thomas (*Journal*, May 9, p. 1052) in replying to my letter (*Journal*, April 4, p. 780) has found it necessary to base his criticism on a flagrantly inaccurate paraphrase of my words. I did not, as suggested by Dr. Thomas, claim that "the majority of authorities are in favour of *x*-ray epilation for *M. canis* ringworm." My actual words were: "Most authorities agree that topical treatment may prove inadequate in some cases of *M. canis* ringworm" and in this connexion I would refer Dr. Thomas to Duncan,[1] Ormsby and Montgomery,[2] and Sharp.[3]

Dr. Thomas explains that the "frequency of erythema reactions and also of coincident glabrous skin involvement as a means of diagnosing *M. canis* scalp infections" renders examination by Wood's light unnecessary. This is not in accord with the observations of other investigators. Beare and Cheeseman[4] and Havyatt[5] found that little or no inflammation was present in approximately half of the cases examined by them. Furthermore, *M. canis* scalp infections are not invariably associated with glabrous skin involvement. In consequence, I contend that the use of Wood's light in the diagnosis of *M. canis* scalp infections can hardly be dismissed as "unnecessary." If, as would appear to be the case, Dr. Thomas relied on simple clinical inspection of the school populations referred to in his article and omitted Wood's light examination in assessing the "cure" in his series of 24 cases, it would seem that his conclusions can at best be regarded as of doubtful validity.—I am, etc.,

Glasgow, W.2. W. A. DEWAR.

REFERENCES

1 *Modern Trends in Dermatology*, 1948, edited by R. M. B. MacKenna. Butterworth and Co. (Publishers), Ltd., London.
2 *Diseases of the Skin*, 1948, 7th ed. Henry Kimpton, London.
3 *Aust. J. Derm.*, 1951, **1**, 138.
4 *Brit. J. Derm.*, 1951, **63**, 165.
5 *Aust. J. Derm.*, 1952, **1**, 239.

Intestinal Reflux into the Bile Passages

SIR,—I should like to record the following case.

A frail lady of 71 was admitted with four days' history of central abdominal colic, vomiting, and intermittent abdominal distension. Four years before, a cholecystogram showed a failure to concentrate dye. Cystectomy had been advised but refused. Since then she had had mild recurrences of symptoms at intervals of a few months, the last attack being six months before admission to hospital.

Examination of the abdomen showed slight distension, no tenderness, presence of bowel sounds and waves of peristalsis from left to right across the upper sector. Splashing was elicited in the upper abdomen, while recumbent. A small left femoral hernia was reduced. Clinical findings suggested a pyloric stenosis. After a barium meal stomach and duodenum appeared normal, and barium passed as far as the ileum. Remarkably, however, the biliary tract filled with barium, outlining the common and hepatic ducts, and finer branches, in excellent detail (see illustration). The gall-bladder did not appear to fill.

The patient's condition was poor, and laparotomy was performed without delay. The obstruction in the small gut was not, as expected, a gallstone but a Richter's hernia in the neck of the left femoral canal. This was reduced. The patient's condition did not allow further exploration. There were no obvious adhesions in the upper abdomen. Recovery was uneventful except for tenderness over the liver for several days and a little pyrexia for about a week. A cholecystogram was done two months later. The gall-bladder concentrated poorly and emptied rapidly without the stimulus of a fatty meal. There was no indication of any abnormal communication between the biliary system and gut.

The interesting feature of this case was that *x*-ray examination after a barium meal showed a reflux of intestinal contents into the biliary passages. The clearness of the outline suggested that fluid had entered under slight pressure, presumably through a freely patent communication. The gall-bladder did not share in the reflux. The patient's mild symptoms did not suggest the earlier passage of a gallstone through the common bile duct. If a gallstone had quietly eroded its way into the small bowel from the gall-bladder, it is improbable that a widely open fistula would have persisted, and neither barium meal examination nor subsequent cholecystogram lent any support to this. On the other hand, a reflux of intestinal contents through the sphincter of Oddi may have occurred. The presence of an obstruction in the small bowel at the time, and the demonstration of a rapidly emptying gall-bladder subsequently, lend support to this. A subsequent barium meal was normal, and there was no evidence from the report of a barium meal four years previously of any reflux.

Should the diagnosis of retrograde flow into the common duct be correct, it raises the interesting possibility of this as a cause of cholangitis in obscure cases of cirrhosis.

My thanks are due to Mr. F. J. C. Matthews, under whose care the patient was admitted, for permission to publish this case, and to Dr. G. A. MacDonald and Messrs. Murphy, of the radiological department, for the *x*-ray investigations.—I am, etc.,

Coventry. I. A. HARRIS.

Importance of Post-mortem Examinations

SIR,—In my experience, which extends to nearly 30 years in general pracice, it is very rarely that the family doctor is informed even of the time at which a necropsy is to take place, let alone receives a report on the result—which in my case I can never remember happening. Is it not therefore time that someone was made responsible for seeing that this information was conveyed to the family doctor, for it is probably not always possible for him to attend in person? After all, he is much concerned in the matter. He may have attended the patient for many years, and he was in all probability called when the death took place. Furthermore, it was probably his decision that led to a post-mortem examination being carried out.

Post-mortem examination would no doubt sometimes throw interesting sidelights on the accuracy or otherwise of our diagnoses. Recently, when a myxoedematous woman of 75 died suddenly, and when perhaps a diagnosis of cerebral haemorrhage or coronary thrombosis would not have been unreasonable, the extreme and unusual pallor of the face, even in the dim light of the little scullery in which she was lying, led me to suggest that a post-mortem would be desirable. This eventually showed that my patient had, in actual fact, died of a ruptured aneurysm of the abdominal aorta; and this aneurysm was, in some way, probably the cause of the abdominal pain of which she had complained to her family for a fortnight before her sudden death.

In view of what Dr. F. E. Loewy (*Journal*, May 23, p. 1163) says upon the need for post-mortem examinations, one would like to ask him whether he is aware of the natural repugnance of people generally to post-mortem examinations on their deceased relatives. It is all very well to talk about the needs of medical science and educating the general practitioner. These are as nothing beside those feelings of sentiment and affection which are to be found in the generality of ordinary people.—I am, etc.,

Hove. G. L. DAVIES.

Adrenaline Cream

SIR,—I have read with great interest the report (*Journal*, May 16, p. 1085) from the Walkden Clinic on the assessment of massage with adrenaline cream in the treatment of rheumatic disorders. At least one fact has emerged—that adrenaline cream has a definite therapeutic value as a palliative, thus refuting the findings of the Research Committee of the Empire Rheumatism Council, reporting on the controlled tests on 39 cases in all investigated at nine different centres in 1951. There are, however, certain observations I would like to make, as it is important to show why the results in recovery time obtained in this otherwise well-conducted trial differ from others previously reported (Moss[1] and Howell[2]).

It is a minimal dose of adrenaline acting *in* the skin that relieves muscle spasm and pain. I would refer future investigators on this subject to the work of Danielopolu[3] on the double and antagonistic action of adrenaline in very weak concentrations on the intersympatho-parasympathetic mechanism, of Pasteur Vallery-Radot and Holzer[4] and Morin[5] on similar experiments using exceedingly weak concentrations of adrenaline, showing that it has a *reversible* action. I was therefore surprised to read that an adrenaline cream five times more concentrated than the one I have always employed has been used by this clinic in these tests.

In an assessment of recovery time the Walkden Clinic has based its trials on an early paper submitted to the *Lancet* in July, 1946, and published in the *Medical World* in 1949,[1] and which dealt mainly with the treatment of "primary fibrositis." In all subsequent papers I stressed that all cases of osteoarthritis and cases of rheumatoid arthritis (the latter only treated in the rehabilitation stage) need a special technique of joint immobilization to get good results. I quote "patients should be treated daily in their homes and in their bed for the first few days. Freedom from pain and increased movements round the affected joints are so marked, after five minutes of treatment, that if active movements are allowed a most severe 'tissue reaction' will follow (due to the stretching of muscular tissues and adhesions) after the 'anaesthetic' effect of the cream has passed off" (Moss[6]).

This technique has not been used and these cases have been treated only three times a week at an out-patient clinic, and, in all probability, walked home after treatment. It is not surprising that these patients took twice as long to recover compared with those treated with a simple cream which does not cause immediate relaxation and more freedom of movement. The treatment of disk lesions with adrenaline cream has never been suggested in any of my papers. The exciting factor in this condition causing pain and spasm is far too powerful to be beneficially influenced with adrenaline cream.

It would therefore appear that fully 60% of the cases treated for an assessment of recovery time with adrenaline cream (10 cases of disk lesions, seven cases of osteoarthritis, two cases of rheumatoid arthritis) have been treated by methods that would cause greater pain and further disabilities and delay considerably the recovery time and thus lead to a wrong assessment of the series as a whole.

The similarity of the findings with dry massage and adrenaline cream is of particular interest. It would appear that some "substance" is formed in the skin that blocks the pain chain mechanism. The theory advanced that the mode of action of the minute dose of adrenaline can be explained by systemic absorption has been discarded by the writer. If adrenaline cream is applied without massage to the skin (previously rubbed for a few seconds with a damp towel to remove surface impurities and weaken the horny layer) within a very few seconds pain is greatly relieved and the muscle can be felt to be relaxed. (Incidentally, the use of a simple cream will not have the slightest effect on pain or spasm.)

Furthermore, acting on my theory that it is very weak concentrations of adrenaline acting in the skin that produce these results, during the past 18 months I have been using intradermal injections of adrenaline 1/100,000 in association with adrenaline cream for the treatment of cases of rheumatoid arthritis—only in the rehabilitation stage—in cases of osteoarthritis and in those cases of fat and thick-set patients who suffer from primary fibrositis and who do not respond well to treatment with adrenaline cream (Howell[2]). Given subcutaneously, these injections have not the slightest effect upon pain or muscular spasm. Injections, in minimal doses into the skin, over the myalgic spots and referred areas of pain act almost within a second in the relief of pain and muscle spasm. It would be of interest to discover the weakest concentration of adrenaline that would have this effect.

A preliminary paper on this new technique, "Adrenalinotherapy Associated with Skin Therapy in the Treatment of Rheumatic Disorders," was the subject of a lecture demonstration that I gave to the Société des Praticiens de Paris on April 16 last.[6]—I am, etc.,

London, W.1. LOUIS MOSS.

REFERENCES

1 *Med. Wld (Lond.)*, 1949, **70**, 244.
2 *Lancet*, 1950, **2**, 395.
3 *Presse méd.*, 1947, **55**, 214.
4 *C.R. Soc. Biol. (Paris)*, 1944, **138**, 742.
5 Ibid., 1944, **138**, 611.
6 *Med. Wld (Lond.)*, 1951, **75**, 288.
7 *Med. Press*, 1950, **223**, 515.
8 *Clinique (Paris)*, 1953. In press.

Subcostal Pain Following Controlled Respiration

SIR,—Dr. T. T. Currie's medical memorandum (*Journal*, May 9, p. 1032) raises one or two important points. I was disturbed to read of the high incidence of apnoea lasting 5–10 minutes following the administration of both succinylcholine and gallamine triethiodide for such procedures as dental operations. I presume, although Dr. Currie does not specifically say so, that succinylcholine was given by the single-injection technique. Succinylcholine response varies so markedly from patient to patient in the lower-dose ranges (20–40 mg.), as far as both relaxation and apnoea are concerned, that I have largely abandoned this technique of single injections. I believe it to be a much more rational approach to titrate, as it were, the drug against each patient by the use of the continuous intravenous infusion of dilute solutions of succinylcholine, even when relaxation is needed for tracheal intubation only. In this way, excellent relaxation can be achieved with the minimum of succinylcholine for that particular patient, and with the avoidance of apnoea

in the very large majority of cases. If it does occur it is of extremely short duration (30 seconds or so). Although apnoea holds no dread for the well-trained anaesthetist, we must not lose sight of the fact that it is essentially an unphysiological state of affairs, as is the positive-pressure artificial respiration which must be instituted to maintain ventilation. Under certain circumstances, such as "bucking," straining, and irregular patterns of respiration, manual respiration may be the lesser of two evils, but, on the whole, apnoeic states should be avoided unless specific indications exist.

My second point is one of semantics. "Controlled respiration" by our definition is that state wherein spontaneous respiration has been abolished by means of hyperventilation with oxygen, maximum elimination of carbon dioxide, overdistension of the lungs (inhibition of the Hering–Breuer reflex), and a varying degree of central respiratory depression, but in which spontaneous respiration will resume soon after manual ventilation has been discontinued. Paralysis with muscle-relaxants clearly does not come within this definition, as spontaneous respirations will not resume as long as the drug maintains its paralysing effects on the muscles of respiration and in particular the diaphragm. This type of respiration should be called what it has always been called—namely, "artificial respiration." The borderline between controlled and artificial respiration is not always too clear, and one may blend into the other; this occurs not infrequently after controlled respiration has been maintained for prolonged periods. Artificial respiration may not be as well-sounding a term as controlled respiration, but it is scientifically more correct in the case of apnoea from muscle-relaxants.—I am, etc.,

Chicago. GORDON M. WYANT.

The Floating Spleen

SIR,—The case of a pedunculated cystic spleen described by Dr. A. H. Bartley (*Journal*, May 23, p. 1167) is so strikingly similar to a case of mine operated on in Northern Malaya some years ago that an interesting problem is raised.

This patient, a Malay woman of about 30 years, presented with a history of intermittent abdominal discomfort and a tumour so mobile that it was thought to arise from the pelvis. At operation a spleen measuring approximately 20 by 10 cm. was drawn out of the abdomen on a ribbon-like pedicle, the clear glossy surface of the organ being embossed with thin-walled cysts up to 4 cm. in diameter. Later, when the organ was cut, it was found that the bulk of the splenic tissue was replaced by isolated cysts as smooth inside as they were outside and containing clear straw-coloured fluid. There were no obvious cysts in the liver.

The point, then, is this. Is a cystic spleen more prone to become pedunculated than is the normal organ? Or do cysts develop secondarily in a mobile spleen through intermittent torsion of its pedicle?—I am, etc.,

Dundee. J. F. RILEY.

Orthopaedics and Its Name

SIR,—There is a time when the original and accepted name given to a subject is no longer adequate or accurate and might usefully be changed. I feel this applies to the word orthopaedics, or -pedics in America. No doubt it has a good Greek origin from "the straight child" and I suppose was first applied to the correction of mechanical deformities in children. But now the subject covers a multitude of physical and mechanical disorders from the neck to the toes, and the name has long appeared inappropriate. This distortion of the meaning of words has been brought home to me recently by reading a most useful book entitled *Chiropodial Orthopaedics*—hands, feet, straight, children. This book is entirely devoted to adult feet. I gather that American "podalists" would be insulted by being called chiropodists, as the latter word stinks to them of chiropraxis.

But it is the word orthopaedics with which I am concerned. Why not orthosomatics, or some more accurately descriptive word? It could quickly and readily replace the present word and would have an accurate meaning and sound well in the medical directory or telephone book. I feel seriously about the misuse of words, and wonder if the "orthopods" will agree to become "orthosomes" to their friends.—I am, etc.,

London, W.1. R. D. LAWRENCE.

POINTS FROM LETTERS

Services Tobacco Concession

Dr. G. C. PETHER (Hitchin) writes: I recently examined for a job a youth of 20 years. He had just come out of the Army. He described attacks of bronchitis at intervals and also how he had smoked 180 cigarettes weekly while in the Services. He was still smoking 100 and was unable to calculate what it cost weekly or yearly. I took some trouble to instruct him in simple methods of calculation, which he had never learned at school. I submit that this "concession" of low-cost cigarettes is stupid, unnecessary, and most harmful to the exchange position, leaving the person supposed to benefit in worse health, reduced in pocket and even, as this case shows, incapable of estimating his outlay. Should not the Services sell tobacco at normal rates to those who want it, give a cash allowance in lieu, and spend a little more time in teaching simple arithmetic to those who need it?

Smoking and Cancer

Mr. GERALD SOLOMON (Manchester) writes: It is interesting to note that the statistics which are being used to show a relationship between lung cancer and tobacco smoking show that pipe smokers appear to be less likely to develop the disease than cigarette smokers. There is one implication of this state of affairs which I have not yet seen mentioned anywhere, but which does, I feel, merit investigation. The continual presence in the smoker's mouth of the stem of his pipe will surely stimulate the secretion of large volumes of saliva. Is it not possible that this solution takes up a carcinogen (or co-carcinogen) which the cigarette smoker inhales and the pipe smoker swallows? It would be interesting to see whether the incidence of carcinoma of the stomach is higher in pipe smokers than in cigarette smokers and non-smokers.

Barbiturate Poisoning

Dr. E. MACKERNAN (Birmingham) writes: In view of the increasing number of attempted suicides and cases of accidental poisoning by barbiturate tablets, capsules, etc., would it not be possible for the manufacturers to add 1–2 grains (65–130 mg.) of ipecacuanha to each so that in the event of a lethal dose of the former being consumed the emetic properties of the latter would take effect and the poison automatically vomited up? I believe some years ago I read a letter in the *Journal* from a Colonial member who adopted this method in his own dispensing practice.

Litigation Against Doctors

Mr. C. J. CELLAN-JONES (Swansea) writes: I agree with Mr. William Gissane (*Journal*, May 23, p. 1167) that increasing litigation against doctors menaces sound clinical medicine. Moreover, the happy relationship and the feeling of confidence which existed between the doctor and his patient are being replaced by mutual distrust. Recently, on reaching the theatre a patient said, as he waved an accusing finger at me: "They knocked my elbow as they wheeled me in. It may be nothing, but remember that I have warned you." The atmosphere of the operating-theatre is not improved nowadays by the gloomy thought that the surgeon, the anaesthetist, and the nursing staff must constantly regard themselves as potential criminals.

Asthma at Sea

Dr. G. L. ALEXANDER (Bristol) writes: In the *Journal* of December 10, 1949 (p. 1357), I commented on the sufferings of asthmatics in tourist liners to Australia. Even those who have not had attacks for months or years previously have frequent attacks during the voyage, and often go into status asthmaticus, which nothing relieves until they get off the ship. It is our experience that they suffer much less in the newer ships. In old ships, however high the standard, there is inevitably more dust from disintegrating paint, furniture, textiles, moulds, etc. Further, they are more heavily sprayed with compounds containing D.D.T. and pyrethrins to keep down cockroaches. I would therefore urge that practitioners should advise any asthmatic patient intending to travel by sea to book only in a relatively new ship, and to get the best first-class cabin they can possibly afford.

Obituary

C. B. LEVICK, O.B.E., M.B., Ch.M., F.R.C.P.

Dr. C. B. Levick, physician in charge of the cardiology department at St. George's Hospital, died at his home at Amersham on May 31 at the age of 56. He will be remembered first and foremost as a wise general physician. He was also a good teacher and skilled administrator.

Claude Blaxland Levick was born in New South Wales, Australia, in 1896. He was educated at Sydney Grammar School and Sydney University, where he held the Aitken and Cooper scholarships, the latter in classics, and the John West and Grahame medals. He qualified M.B. at Sydney in 1920 and Ch.M. in 1922. He then came to England, where he held house appointments at the Manchester Royal Infirmary before finally settling in London. Here he held a number of resident appointments at St. George's Hospital and at the Victoria Hospital for Children, Tite Street. In 1925 Levick was elected physician to out-patients at the Victoria Hospital and, in 1928, assistant physician to St. George's Hospital. His two main interests were in cardiovascular disease and diseases of children. He was one of the earlier physicians to use the electrocardiograph in clinical practice, and acquired remarkable skill in interpreting the standard leads. He always remained, however, a general physician, and saw each problem against the background of the whole patient; it was this, together with a remarkable care for detail, that made him such a valuable consultant.

Levick had a high reputation as a teacher, and instilled into his students a regard for fundamental facts which they never forgot. A keen and wise person, he was the most generous and helpful of colleagues, and a friend to his juniors.

C. P. P. writes: I knew Blaxland Levick for the 30 years he was associated with St. George's Hospital. He was a house-physician when I first came to St. George's, and was an excellent teacher with a precise mind: his students were trained to think and express themselves precisely and clearly. Later when he became resident assistant physician he showed that he was a first-class administrator, and this was constantly demonstrated throughout his life—both before and after the war with his advice over hospital matters and in committee, and during the war with the success that came to him in his Middle East appointment. Blaxland was a shy man, but as a friend he showed a variety of interests. In his early days at St. George's he was an enthusiastic skater and was often on the rink at Grosvenor House before the day's work began. He was a keen lawn tennis and squash player. He was fond of good music and had a large collection of classical records. He will be sadly missed by his colleagues and friends, with his sense of humour and devotion to work which remained until the end.

E. T. ROBERTS, M.D., F.R.C.P.Ed., F.R.F.P.S., D.P.H.

We record with regret the death of Dr. E. T. Roberts at his home at Portsmouth on May 11 at the age of 88. Appointed in 1909 on the inauguration of the school medical service as principal medical officer to the School Board (later the Education Authority) of Glasgow, he served in that city for over 20 years until his retirement at the end of 1929.

Born at Worcester, where his father was in practice as a solicitor, on April 24, 1865, Ernest Theophilus Roberts was educated at the cathedral and grammar schools there and then went on to the University of Edinburgh, where he graduated M.B., C.M. in 1886, proceeding to the M.D. in 1889. After experience as resident physician and assistant (by competitive examination) to the professors of clinical medicine at the Royal Infirmary, Edinburgh, and as senior medical officer of the Children's Hospital and the City Fever Hospital, Birmingham, he entered general practice in 1892 at Keighley, Yorkshire, where he succeeded his uncle, Dr. Arthur Roberts, who then moved to Harrogate.

His interest in public health and children's diseases led him in 1909 to enter the field of school medicine at Glasgow, where under his guidance a comprehensive scheme of medical inspection and treatment was built up, including the provision of 10 special schools, mostly of the open-air type, for physically and mentally defective children as well as numerous special classes for blind, deaf, and myopic children. Exceptionally gifted and fond of study, he obtained the Cambridge D.P.H. in 1911 and the F.R.F.P.S. in 1918. He became a Member of the Royal College of Physicians of Edinburgh in 1929, and was elected Fellow in 1937. After retirement and at the age of 70 he passed the examination for the diplomas of M.R.C.S., L.R.C.P. in 1935 at the first attempt. He was examiner in public health for the Scottish triple qualification; for the Diploma in Public Health of the Scottish Conjoint Board; and in State Medicine for the F.R.F.P.S. When he retired in 1929 his staff, which was responsible for the health of nearly 190,000 children, numbered 14 medical officers, 5 dentists, and 70 school nurses. He was an honorary member and past president of the Association of School Medical Officers of Scotland. During the war of 1914–18 he served as a captain in the R.A.M.C.

Ernest Roberts was a handsome man of great personal charm. His wise counsel and ripe experience were at all times available to those who sought his help, while his quiet and never-failing courtesy endeared him to everyone. He had wide interests in church and social work, and was an eloquent speaker. He married Miss Rosa May Paddock, the youngest daughter of the late William Paddock, of Caynton Manor, Newport, Shropshire, in 1892, and Dr. and Mrs. Roberts celebrated their diamond wedding anniversary last year. Their son, Dr. T. E. Roberts, is medical officer of health for Portsmouth, and their daughter married Dr. J. C. Eaton, of Glasgow.—J. T. G. E.

HILDA J. GARDNER, M.B., B.S.

Dr. Hilda Gardner (née Florey) died on May 18 in the Royal Melbourne Hospital—the hospital which she served from the time of her appointment to the position of assistant bacteriologist in 1929.

Hilda Josephine Florey was born in 1890 at Malvern, South Australia, the daughter of Joseph and Bertha Mary Florey. She was one of a distinguished family, of whom her brother, Sir Howard Florey, is the best known. After leaving Miss Thornber's School for Girls in South Australia, she entered the University of Adelaide in 1908, and graduated M.B., B.S. in 1912. Her undergraduate course was brilliant: she occupied first place in her course for four of the five years, including the final year. Between 1913 and 1917 she held resident appointments at the Adelaide Hospital, the Adelaide Children's Hospital, and the Women's Hospital, Melbourne. In 1917 she married Dr. John Forrest Gardner, of South Australia, who practised at Richmond, Victoria,

where he died in 1928. After her husband's death Dr. Gardner returned at once to professional practice and joined the staff of the then Melbourne Hospital as assistant bacteriologist, a position she occupied until 1934, when she was appointed bacteriologist and serologist to the Royal Melbourne Hospital. In 1951 she was awarded an honorary fellowship by the Royal Australasian College of Physicians in recognition of her distinguished service to Australian medicine.

Her career was characterized by an unswerving devotion to the fulfilment of her responsibilities, which, combined with her professional skill, brought her rapidly into the front rank of Australian clinical pathologists. Dr. Gardner made haematology her principal interest and study. Her opinion was always thoughtfully considered before being offered, and was supported by strict attention to the details of the case. Clinicians sought her advice because of these attributes. Alone, or in collaboration with others, she contributed many original papers, which, taken altogether, cover the fields of haematology and bacteriology in the widest sense. Her most important contributions, however, were not those she could record in medical journals.

Hilda Gardner's professional work invariably remained her first consideration, but, like every other great person, she maintained wide extramural interests. A sensitive discrimination, coupled with a keen appreciation, distinguished her contributions to artistic design; in other circumstances she might have contributed even more as expressions of her ideas.

She continued with her work to the end in the face of serious ill-health. It was typical of her courage that she spent her last hour in consultation about one of her patients. She is survived by her daughter, Dr. Joan Gardner, of the University of Melbourne.—J. H. L.

Sir ROBERT G. ARCHIBALD, C.M.G., D.S.O., M.D.

We are indebted to Sir ERIC PRIDIE for the following appreciation of the late Sir Robert Archibald, whose obituary notice was printed in the *Journal* of May 16 (p. 1112): Sir Robert Archibald established a personal reputation, which later became a tradition in the Sudan, for his devotion to duty, his consideration for others, and for inspiring men to try to follow in his footsteps. I first met him during the later stage of his Sudan career, when he had an international name in tropical medical research. His never-failing readiness to help those who needed his assistance, his enthusiasm for and brilliance in his work, and his deep sympathetic understanding of Sudan problems and of the Sudanese people made him the friend of all, deeply respected throughout the country. It was characteristic of him that after retiring from the Sudan he took charge of Chacachacare leper settlement in Trinidad. There can be few men who have exercised so great an influence over those with whom they have been associated, and Archibald's name will long be remembered with gratitude and admiration in the Sudan, which he served so faithfully, as representing all that is best in the British way of life.

Dr. MAXWELL SMELLIE died suddenly at sea on May 7 while on a voyage to the Far East and was buried at sea on May 8. Maxwell Smellie was born on January 10, 1902, at Hamilton, Lanarkshire, where his father was later to be provost. He was educated at Hamilton Academy and at the University of Glasgow, qualifying by taking the Scottish triple qualification in 1931. He was a keen and active footballer, and captained the University's Association football team when it won the Scottish amateur cup. During the play in the final tie he sustained a fractured leg, and the consequent plating of the limb caused him a certain amount of permanent inconvenience. His interest in the game, however, never declined, and he became president of the Dagenham Football Club. For over 20 years he practised in Dagenham and was a well-known and respected figure, a popular doctor, and a friend to many. During the last war he was a captain in the Home Guard and devoted all his leisure time to his unit. He returned to his native Scotland last year and before settling down decided to gratify his intense love of the sea. To his widow, sons, and daughter our deep sympathy is extended. Dr. Smellie's death will be keenly felt by all those who knew him or came into contact with him.—B. K.

Mr. E. R. DESOUTTER, whose light engineering firm until a few years ago was famous for the manufacture of artificial limbs, died on May 11 at the early age of 51.

We are indebted to Mr. K. I. NISSEN for the following appreciation: The death of Mr. Emile Robert Desoutter will be regretted by many surgeons and by thousands of patients who have worn the artificial limbs of that famous *marque de fabrique*. The Desoutter family have a remarkable record in modern engineering design and practice. As boys, Emile Desoutter and his four older brothers were all trained by their father in the art of making watches and repairing every type of antique timepiece. However, in 1912, one of them, Marcel, lost a leg in a flying accident, and it was the successful light-metal above-knee limb fashioned by another brother, Charles, that led rapidly to the establishment of an industry which flourished during and between the two wars and which set a new high standard of technical perfection in lower limb prostheses. Mr. Desoutter joined three of his brothers at the age of 19 and played an active part in the development both of the artificial limbs and of the light-weight pneumatic and electric tools which were at first designed for their assembly. He took part in the firm's unfortunate controversies with the Government of the day which arose first in 1933 and later in 1948, when he had reluctantly to discontinue the manufacture of artificial limbs. Among surgeons in general Mr. Desoutter will long be remembered for the keen personal interest he took in the fitting and training of amputees, particularly young children with congenital defects; for his support of surgeons practising the modified Syme's amputation; for his adaptation of a pneumatic tool to the needs of orthopaedic surgery, and for the sturdy electric plaster-saw now in general use in Great Britain. Those who knew him personally will remember his generous and kindly nature and his capacity for friendship. As the last of the four brothers of the original firm Mr. Desoutter latterly had heavy responsibilities, which were lightened by a very happy family life in the country at Little Gaddesden in Hertfordshire. His death came most unexpectedly, some ten days after a spinal operation, from which he appeared to be making a rapid recovery. He leaves a widow, a daughter, and two sons, one of whom is carrying on the engineering tradition of the family.

We record with regret the death at Shanklin on May 20 of Mr. J. A. GAYNOR, senior surgeon at the Royal Isle of Wight County Hospital, Ryde. He was 52 years of age. Joseph Alfred Gaynor was born on March 19, 1901. He studied medicine at Trinity College, Dublin, graduating M.B., B.Ch. in 1923, and winning the Houghton clinical medicine prize and prize for surgery at Sir Patrick Dun's Hospital in the same year. After graduation he went out to Newfoundland, where he was house-surgeon at the General Hospital at St. John's. When he returned to Britain he took the F.R.C.S.I. and settled in Shanklin, where he was surgical member of a group practice until the Health Service came into operation. Besides his appointment at the County Hospital, Gaynor was a consultant surgeon to the Shanklin Cottage Hospital and the Frank James Hospital, East Cowes.

We are indebted to H. S. H. W. for the following appreciation: It is difficult for one who has been a colleague and friend of Alfred Gaynor for over twenty years to write

of his passing at the early age of 52, when he was at the zenith of a brilliant surgical career. Benefiting from a sound surgical grounding at Trinity College, Dublin, and for many years at Shanklin, from the vast experience of John Cowper, doyen of Isle of Wight surgeons, Gaynor quickly gained the esteem and trust of practitioners throughout the island. After the death of Mr. A. A. Straton in an air raid during the last war Gaynor found himself, at an unusually young age, senior surgeon at the Royal Isle of Wight County Hospital, Ryde. He was of a cheerful and sympathetic disposition, and his Irish humour and sparkle endeared him to his many patients. He will be greatly missed, not only in his home town but throughout the island. To his colleagues his loyalty and helpfulness were invaluable. He never spared himself, and to every general practitioner with whom he came in contact he proved a friend and counsellor. His fortitude during a long and painful illness was an inspiration and example to us all.

DR. PERCIVAL GEORGE QUINTON, who died suddenly on May 21 at the age of 59, received his medical education at University College Hospital and qualified M.B., B.S. in 1918, proceeding to M.D. in 1921 after service in the R.A.M.C. with the British Army of the Rhine. He was superintendent of St. Mary's Hospital, Paddington, before joining in 1924 the staff of the Royal London Homoeopathic Hospital, with which he was connected during the remainder of his professional career. At the time of his death he was physician with charge of out-patients and medical officer to the nursing staff, as well as secretary of the medical advisory committee of the hospital. He was a Fellow of the Faculty of Homoeopathy, which he served in many capacities, including that of secretary. He was in turn assistant editor of the *British Homoeopathic Journal*, hon. librarian, and vice-president. Dr. Quinton was a skilful physician, beloved by his patients and colleagues. He was also a pianist of talent and a good linguist—a gift which led him to a study of the methods of the French school of homoeopathy as represented by Dr. Leon Vannier. He was elected a vice-president of Le Centre Homoeopathique de France, and represented his colleagues in the United Kingdom at many congresses abroad. Two daughters survive him, one being a member of the medical profession.—W. R. McC.

Universities and Colleges

UNIVERSITY OF LONDON

The governing body of the British Postgraduate Medical Federation has approved the award of Postgraduate Travelling Fellowships for 1953–4, tenable for one year, to M. B. McIlroy, M.D., M.R.C.P., of St. Bartholomew's Hospital (respiratory function, U.S.A.); D. Marrack, M.D., of the Postgraduate Medical School of London (biochemistry, U.S.A.); T. A. J. Prankerd, M.D., M.R.C.P., of University College Hospital (haematology, U.S.A.); and P. Story, M.D., of St. Bartholomew's Hospital (haematology, U.S.A.).

J. A. V. Butler, D.Sc., has been appointed to the Chair of Physical Chemistry tenable at the Institute of Cancer Research (Royal Cancer Hospital), from January 1, 1953.

Professor J. M. Mackintosh has been nominated for reappointment as the representative of the University on the governing body of the Slough Industrial Health Service.

The following have been recognized as teachers of the University in the subjects indicated in parentheses: *Charing Cross Hospital Medical School*, Mr. L. R. S. Taylor (Oto-rhino-laryngology); *Institute of Neurology*, Mr. Harvey Jackson (Neurosurgery); *Westminster Medical School*, Mr. P. D. Trevor-Roper (Ophthalmology); *Institute of Dental Surgery*, Dr. C. F. Ballard (Dental Surgery (Orthodontics)). Mr. A. G. Leigh, who is already recognized as a teacher of ophthalmology at the Institute of Ophthalmology, has been recognized also as a teacher of ophthalmology at St. Mary's Hospital Medical School.

The degree of D.Sc. has been conferred on Professor A. D. M. Greenfield, Dunville Professor of Physiology in Queen's University, Belfast, and on Professor C. L. Oakley, Brotherton Professor of Bacteriology in the University of Leeds.

Medico-Legal

VICARIOUS LIABILITY

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

In recent years some legal decisions on the allocation of responsibility between hospitals and doctors have provoked disquiet in the medical profession. Some medical men consider that the holding of a hospital authority to be vicariously responsible for a doctor's mistakes will diminish his sense of responsibility and his independence of professional action. And, some have added, the natural tendency of the hospital authority will be to try by rules and regulations to minimize the possibility of error by the doctor. The converse view has also been expressed that, if hospital authorities are not to carry the responsibility for errors made by their junior medical and surgical officers, the morale of these men will suffer and applicants for hospital posts will be hard to find.

If either or both these views are right, then the effect of the present state of the English law will be disastrous both for the profession and for the community, which the profession exists to serve. It is therefore important to examine whether these views result from a failure to appreciate the true nature of the principle of law concerned, or whether the law is such as to justify them. If it is, then the sooner it is changed by Parliament the better.

Acts of Servants and Agents

The responsibility of the governing bodies of hospitals for the acts of their agents is one of the many examples of the fundamental principle of English law—*qui facit per alium facit per se*. In anything he does a man must take reasonable care not to harm his neighbour. His neighbour is anyone who he ought to realize will be affected by that particular activity. If a person chooses, or is obliged by circumstances, to carry out the particular activity through the medium of someone else, whether the someone else is in his employment as a servant or simply engaged as an agent to do that particular thing, that person cannot thereby divest himself of the duty to take reasonable care not to do his neighbour harm. And if the servant or agent fails to take reasonable care, and in fact does harm, not only is he personally responsible, but the employer is vicariously responsible also.

The owner of a ship that carries passengers from Capetown to London is accordingly under a duty to exercise reasonable care towards them in doing so. This is an activity which he cannot carry out himself. He employs the master of the ship to navigate her as far as Dover. From Dover to Tilbury he employs a Port of London pilot with the necessary specialist knowledge of the Thames and its estuary. The master of the ship is his servant; the pilot is his agent to pilot the ship on that particular voyage up the river. If the ship is cast away and the passengers are injured through the failure of the master to exercise reasonable care in navigating the ship between Capetown and Dover, or the failure of the pilot between Dover and Tilbury, the shipowner is in law just as responsible to the injured passengers as is the pilot or the master. The fact that he is vicariously responsible in no way diminishes the personal responsibility of his servant or agent.

In the same way the governing body of any hospital is under a duty to exercise reasonable care towards people in the hospital. This duty is owed not only to the patients but to its own staff. In so far as the patients are concerned, its duty is to exercise reasonable care over their nursing and any treatment which it sets out to give them or operation which it sets out to perform. None of these activities does it carry out with its own hands, any more than does the shipowner with his own hands navigate his ship. Nurses, physiotherapists, radiographers, house-men are all its servants, just as the master is the servant of the shipowners. Consultants, even if honorary and unpaid, are its agents, just

as the pilot is the agent of the shipowner. If the patient is injured through the failure of any one of them to exercise due care towards him according to the current state of medical knowledge and practice, then the hospital is in law just as responsible to the injured patient as is the nurse, the physiotherapist, the house-man, or the consultant whose failure caused the injury. But the fact that the hospital authority is vicariously responsible in no way diminishes the personal responsibility of doctor or nurse.

An Old Principle

There is nothing new about this principle. That it has recently been reaffirmed in its application to hospital authorities has in law nothing to do with the National Health Service Act, 1946, but is purely coincidental. In our report in these columns of the case of *Cassidy* v. *Minister of Health*[1] the original error stemming from *Hillyer* v. *St. Bartholomew's Hospital* in 1909 and its correction have already been described. In Cassidy's case the court was careful to rest its decision that the Minister as hospital authority was vicariously responsible for the negligence of the consultant on the broad principle stated above, not on any particular statutory duty imposed on the Minister or the hospital authority by the 1946 Act. The principle of vicarious liability is as old as the Common Law, and probably originates in the responsibility of the master for the acts of his slave, who had no independent legal standing, but was absorbed in the family which his master represented and for which in primitive legal systems his master had to answer.

The personal responsibility of the agent and the vicarious responsibility of the principal for the same act exist side by side. The practical result is that the injured person can sue one or other or both, and the consideration dictating which he sues is : Which will be able to satisfy any judgment he may obtain ?

Before the era of widespread insurance it was usually the principal who was sued, because it was usually he alone who was worth powder and shot. Where the principal is the hospital authority, and where personal responsibility for the injury rests on a nurse or a physiotherapist or a hospital servant, who is not likely to be wealthy or insured, the hospital authority is the obvious target. Where the personal responsibility rests on the doctor, who is almost certainly insured whether he is a recently qualified casualty officer or a distinguished consultant, it does not matter to the injured person which he sues. If he is in any doubt whether the doctor is insured or where the personal responsibility will be found to rest—and this may be a difficult question—he will doubtless sue both.

Indemnifying the Principal

Sometimes a judge, having found a house-officer personally and the hospital authority vicariously responsible for a disaster, orders the house-officer to indemnify the authority as to the whole or part of the damages and costs. At Common Law an agent for whose fault his principal has been found vicariously liable is bound to indemnify his principal on the grounds that he ought not to fail to use reasonable care when about his principal's affairs. Under the Law Reform (Married Women and Tort-feasors) Act, 1935, where two people are responsible for the damage caused by the same failure to take reasonable care the court has power to order the one which it thinks to be really as well as legally responsible to indemnify the other, or to contribute to what the other has to pay to the plaintiff.

The result is that the plaintiff can sue whichever he thinks fit, and if he gets his judgment against both can execute it against whichever he thinks will be good for the money. His interests are therefore fully safeguarded. As between those legally responsible for the damages, the one who has to pay the plaintiff can, to the extent of the contribution or indemnity which has been ordered against the other, recoup himself from that other, if the other has sufficient assets to recoup him. Moreover, the court has the opportunity to mark where in its view the blame as opposed to the legal responsibility really lies.

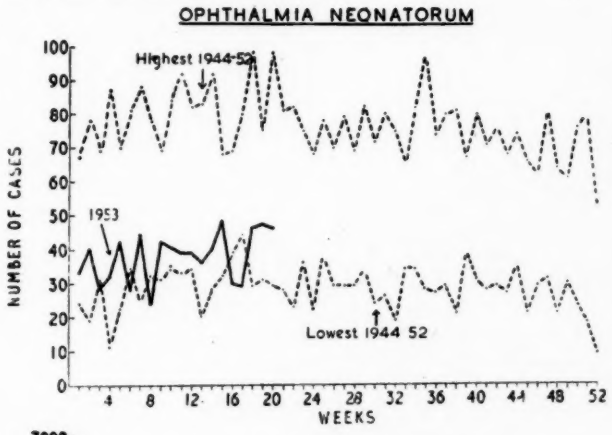
Such then is the state of the law in England, subject to the possibility that the Court of Appeal may hold that by virtue of the provisions of the National Health Service Act, 1946, and the Public Health Act, 1875, hospital management committees cannot be sued for negligence towards their patients at all.[2] But, whatever the law, a doctor's professional standards are imposed on him by the traditions of his profession and his conscience. The sanction for his failures is not that he may get judgment given against him. Since he can insure against the financial implications of a judgment, it does not matter to him financially how the responsibility may be apportioned between him and the management committee. The power of the court to mark where it thinks the blame lies is surely a salutary power. But in the ultimate analysis the relation between doctor and patient, and the standards of conduct the doctor sets himself, must be matters not of law but of conscience.

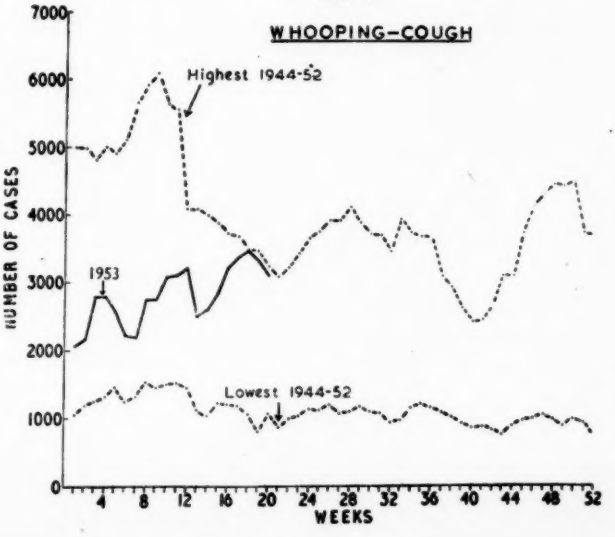
[1] *British Medical Journal*, 1951, 1, 480.
[2] Ibid., 1953, 1, 461.

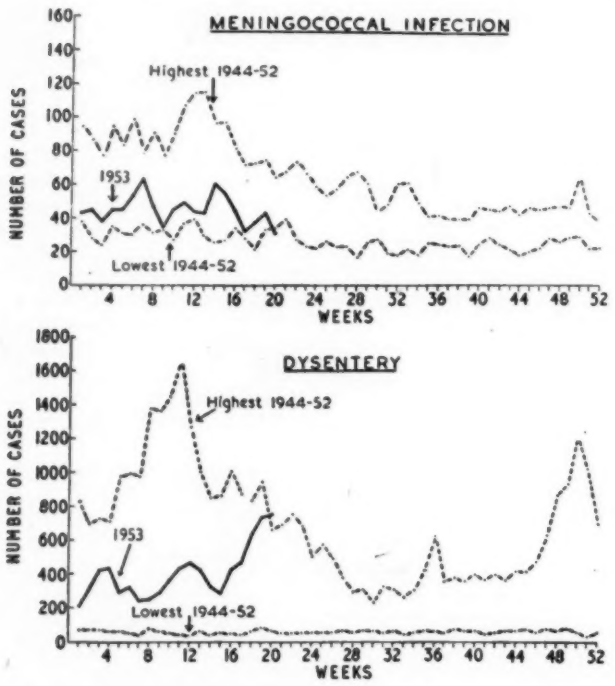
Vital Statistics

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1944–52 are shown thus - - - - - - -, the figures for 1953 thus ————. Except for the curves showing notifications in 1953, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.







Infectious Diseases

Only small variations occurred in the trends of infectious diseases in England and Wales during the week ending May 23. The largest were an increase of 243 in the number of notifications of measles, from 10,034 to 10,277, and a decrease of 209 for whooping-cough, from 3,312 to 3,103.

The largest increases in the incidence of measles were 138 in Lancashire, from 1,489 to 1,627, and 63 in Somersetshire, from 295 to 358; the largest decreases were 102 in Durham, from 387 to 285, 100 in Sussex, from 413 to 313, and 90 in Gloucestershire, from 627 to 537. The largest falls in whooping-cough were 60 in Middlesex, from 219 to 159, 49 in Surrey, from 146 to 97, and 48 in Durham, from 153 to 105. 1,306 cases of scarlet fever were notified, being 20 more than in the preceding week. The largest local variation was an increase of 28 in Yorkshire West Riding, from 108 to 136. 19 cases of diphtheria were notified, 2 more than in the previous week.

29 cases of acute poliomyelitis were notified. These were 3 fewer for paralytic and 4 fewer for non-paralytic cases than in the preceding week. The largest returns were Surrey 5, Yorkshire West Riding 5 (Doncaster C.B. 2, Sheffield C.B. 2), and Essex 3 (Romford M.B. 2).

754 cases of dysentery were notified during the week, 18 more than in the preceding week. This is the fifth consecutive week that the incidence of dysentery has risen. The largest centres of infection during the week were London 123 (Westminster 42, Islington 13, Chelsea 12), Lancashire 78 (Liverpool C.B. 25, Manchester C.B. 13, Preston C.B. 10), Leicestershire 65 (Leicester C.B. 65), Bedfordshire 62 (Luton M.B. 40, Bedford M.B. 16), Durham 46 (Stanley U.D. 37), Norfolk 43 (Great Yarmouth C.B. 26), Essex 29 (Walthamstow M.B. 7), Yorkshire West Riding 29 (Huddersfield C.B. 7), Cambridgeshire 19 (Cambridge M.B. 19), and Northumberland 18 (Newcastle-upon-Tyne C.B. 9).

Week Ending May 30

The notifications of infectious disease in England and Wales during the week included scarlet fever 1,084, whooping-cough 2,476, diphtheria 21, measles 9,012, acute poliomyelitis 52, dysentery 505, paratyphoid fever 8, and typhoid fever 2.

A commentary on the national statistics for the years 1948 and 1949 is published in the *Registrar General's Statistical Review of England and Wales 1948–9, Text, Medical* (H.M.S.O., 10s.). It includes a tabulation of 1949 deaths in accordance with the 1948 International Statistical Classification of causes of death.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **May 23** (No. 20) and corresponding week 1952.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1953					1952				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	19	2	5	1	2	27	6	10	0	1
Dysentery	754	123	93	2	2	328	41	81	2	2
Encephalitis, acute	?	0	0	0		4	0	0	0	
Enteric fever:										
Typhoid	3	0	0	1		1	0	0	0	1
Paratyphoid	4	0	0	0		22	0	1(A)	0	
Food-poisoning	155	15		5		134	17		1	
Infective enteritis or diarrhoea under 2 years				15	25				14	25
Measles*	10,277	345	403	319	331	5,749	320	470	237	404
Meningococcal infection	31	1	12	1		43	2	12	2	1
Ophthalmia neonatorum	46	1	6	0		36	9	9	0	
Pneumonia†	505	34	155	9	5	432	36	208	5	4
Poliomyelitis, acute:										
Paralytic	22	1	3		2	25	0	2	2	1
Non-paralytic	7	0				12	1			
Puerperal fever§	267	30	10	0		245	36	23	2	
Scarlet fever	1,306	88	149	44	66	1,088	65	183	15	36
Tuberculosis:										
Respiratory			161	41				151	31	
Non-respiratory			39	10				23	4	
Whooping-cough	3,103	213	454	53	145	2,905	155	176	102	69

DEATHS in Great Towns	1953					1952				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0		0	0	0		0	0
Dysentery	0	0				0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0			1	0		0	
Infective enteritis or diarrhoea under 2 years	4	0	3	3	1	5		2	1	2
Influenza	4	0	0	0	2	7	2	1	0	1
Measles		0	0		0		0		0	3
Meningococcal infection		0	0				1			
Pneumonia	187	24	14	8	5	195	30		7	12
Poliomyelitis, acute	4	0			0	1	1			0
Scarlet fever		0	0		0		1		0	0
Tuberculosis:										
Respiratory	103	12	14	1	6	141	21	15	5	8
Non-respiratory		1	0	2	1		2	3	0	3
Whooping-cough	2	1	0	0	0	4	0		0	0
Deaths 0–1 year	228	26	31	7	16	211	20	28	3	13
Deaths (excluding stillbirths)	4,935	711	569	111	172	4,926	695	550	99	196
LIVE BIRTHS	8,349	1237	948	246	462	8,228	1277	953	249	424
STILLBIRTHS	211	15	25			172	21	18		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

The Everest Doctors.—The Chairman of Council of the B.M.A. has sent Dr. L. G. C. Pugh the following telegram: "British Medical Association shares general delight at success of expedition and offers you and your medical colleagues warm congratulations."

Anaesthetists Honour Lord Nuffield.—The Faculty of Anaesthetists of the Royal College of Surgeons of England paid tribute to Lord Nuffield's great services to anaesthesia when he was presented with the diploma of Honorary Fellowship of the Faculty at a meeting of the board on June 3. At a luncheon at the Royal College of Surgeons after the presentation, Dr. B. R. M. Johnson, the Dean of the Faculty, proposed Lord Nuffield's health. He referred particularly to the great benefits to mankind which had accrued from the establishment of the Nuffield chair of anaesthesia at Oxford, and to the department of anaesthetic research which was to be housed in the Nuffield College of Surgical Sciences at the Royal College of Surgeons. Wearing the gown of the Faculty which Dr. Johnson had asked him to accept as a gift, Lord Nuffield said that anaesthesia was a subject near to his heart, for he had had some bad anaesthetics in his time. Although his plan to establish the department of anaesthesia at Oxford was not welcomed whole-heartedly at the time, "in Oxford they think to-day that I was right." It was the job of the surgeon to carry out the operation and leave the rest to the anaesthetist. Sir Cecil Wakeley, President of the Royal College of Surgeons, brought the agreeable occasion to a close by calling for three cheers for Lord Nuffield.

Corneal Grafting.—The British Red Cross Society has offered its services for conveying eyes to be used in corneal grafting. Details are given in a recent memorandum from the Ministry of Health (No. 95022/1/16/2, dated May 27). Eyes will usually be conveyed by rail or road, and if hospitals are unable to provide their own transport for any journey or part of a journey assistance from the British Red Cross Society can be obtained on application to the Society's local representatives. For journeys between hospitals and railway stations the Society will provide transport without any charge. For direct journeys between hospitals and the corneal-grafting centres the Society may seek payment from hospitals at the local hospital car service mileage rates. The Society has asked its county branches to get into touch with hospital authorities to settle local arrangements.

Disablement Benefit.—Relaxation of the conditions under which disablement benefit may be paid is the principal proposal of the National Insurance (Industrial Injuries) Bill, 1953. This Bill was presented to Parliament by the Minister of National Insurance, Mr. Osbert Peake, at the end of last month, and the text has now been published. At present disablement benefit can be obtained only if the damage resulting from the accident is substantial (assessed at over 20% disablement) or likely to be permanent. The new Bill allows benefit to be paid for any period during which the disablement is assessed at 1% or more irrespective of whether it is likely to be permanent. The additional cost of this and other changes proposed in the Bill is estimated at £140,000 a year.

Films on Rodent Control.—By arrangement with the United States Public Health Service a remarkable series of films on rats and their control was shown at the Royal Sanitary Institute in London on June 11. The five films, "The Rat Problem," "The Roof Rat," "The Norway Rat," "Rat Proofing," and "Rat Killing," were made by the American Army, with the advice of the Communicable Disease Centre of the American Public Health Service. In order to make the films the rats in a heavily infested building were subjected to the glare of arc lamps for weeks ahead; and to allow every aspect of rat behaviour to be fully displayed the building was sliced in half, down to and below the foundations, and the exposed end covered with glass. The camera could then follow the rats into their burrows. The splendid pictures that have resulted amply repay the trouble taken to get them. One of the best sequences is a close-up of the birth of a litter; another highlight is a fight to the death between a brown rat and a black rat. The technical information is sound, and the only serious criticism is that the poison baits, wrapped in coloured paper, look remarkably like toffees. This could be dangerous if the baits were accessible to children. The films are intended for showing to technical audiences and not to the general public.

"Beauty and Health."—The American Medical Association is co-operating with Druggists Promotion Services, Inc., of Chicago in the production of a new popular health magazine, *Beauty and Health*. This 48-page magazine will be distributed by druggists to their customers. It will publish health educational articles and will stress the dangers of self-medication. Medical information for articles will be supplied by the A.M.A., which will also check copy for medical accuracy. The A.M.A. also publishes its own monthly popular health magazine, which began as *Hygeia* in 1923 and changed its name to *To-day's Health* in 1950.

London's Ambulances.—One section of the London Ambulance Service deals solely with emergency calls. It has 38 ambulances at 18 accident stations. The other and much larger part of the Service is responsible for the routine conveyance of sick persons to and from hospital. Last year the accident section was busier than ever before: it answered 87,691 calls. Of these 13,655 were to street accidents, and on average the ambulances took 7.2 minutes to arrive on the scene. Most of the street accidents occurred between 5 p.m. and 6 p.m. There were nearly 600 calls to attempted suicides, and over 1,600 to victims of assault. In about 5,500 of the calls answered an ambulance was found to be unnecessary. During the year the general section of the Service carried 660,206 patients a total of nearly 3½ million miles. The present strength of the Service is 249 ambulances, 10 ambulance-buses, 39 single-stretcher ambulances, and 21 sitting-case cars.

New Professor at Cardiff.—Dr. Archibald Sutherland Duncan has been appointed the first whole-time Professor of Obstetrics and Gynaecology in the Welsh National School of Medicine (University of Wales) as from October 1, 1953, on the retirement of Professor G. I. Strachan. Dr. Duncan qualified in 1936, and is at present Senior Lecturer in Obstetrics and Gynaecology in the University of Edinburgh and obstetrician and gynaecologist to the Western General Hospital, Edinburgh.

A Jacobite Physician.—The bicentenary of the death of Dr. Archibald Cameron was commemorated by a service at the Queen's Chapel of the Savoy, London, on June 7. Cameron, who is buried in the chapel, was a close friend of Bonnie Prince Charlie and one of the outstanding personalities of the '45. For his part in the rising he was condemned for high treason and hanged at Tyburn on June 7, 1753.

Register of Speech Therapists.—The 1953 *Register of Speech Therapists* has now been published, and can be obtained free on application to the secretary and registrar, Board of Registration of Medical Auxiliaries, B.M.A. House, Tavistock Square, London, W.C.1. Speech therapists are classified on a geographical basis, and, besides address and telephone number, information is given on qualifications, the type of appointment held, and whether private practice is undertaken.

Dr. Bernard Johnson and Dr. Cecil Gray have been re-elected respectively Dean and Vice-Dean of the Faculty of Anaesthetists of the Royal College of Surgeons of England.

Dr. C. Metcalfe Brown, M.O.H. and school medical officer of the city of Manchester, has been elected president of the Society of Medical Officers of Health for the year 1953–4.

Professor H. C. McLaren, professor of obstetrics and gynaecology in the University of Birmingham, has been elected a corresponding member of the Société Française de Gynécologie.

Dr. Melville Mackenzie, a principal medical officer at the Ministry of Health, was elected chairman of W.H.O.'s Executive Board for the session which took place immediately after the Sixth World Health Assembly.

Dr. Julius Lempert, the distinguished American otologist, has received the 1953 Award of Merit of the American Otological Society. Dr. Lempert is an honorary member of the Section of Otology of the Royal Society of Medicine.

Dr. H. E. Sigerist, formerly professor of history of medicine at Johns Hopkins University, is to receive the honorary degree of D.Sc. at the Foundation Day celebrations of London University on November 27.

COMING EVENTS

East Suffolk Division Coronation Dance.—The East Suffolk Division of the British Medical Association is to hold a Coronation Dance at the Seckford Hall Hotel, Woodbridge, on June 24. Tickets (price 15s.) may be obtained from Dr. T. H. Shaw, 23, Henley Road, Ipswich.

Surrey Coronation Ball.—The Coronation Dinner and Ball of the Surrey Branch of the British Medical Association will be held at the Selsdon Park Hotel, Sanderstead, on June 25, at 7.30 p.m. This promises to be a particularly attractive Coronation festivity. Selsdon Park Hotel is an impressive mansion south of Croydon and can be reached within half an hour of the West End of London. The number of tickets is limited and early application is advised. Tickets (price 2 guineas) may be obtained from Dr. L. A. Gibbons, Fulham House, Waterlow Road, Reigate, or from Dr. J. W. Starkey, 9, Lovelace Road Surbiton.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Applications should be made first to the institution concerned.

Monday, June 15

EDINBURGH UNIVERSITY: FACULTY OF MEDICINE.—At Surgery Lecture Theatre, University New Buildings, 10 to 11 a.m., Sir Geoffrey Jefferson, F.R.S.: Variations in Behaviour of Pituitary Adenomas.

●POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Professor T. L. Hardy: Colon Neuroses.

Tuesday, June 16

EDINBURGH UNIVERSITY: FACULTY OF MEDICINE.—At Surgery Lecture Theatre, University New Buildings, 10 to 11 a.m., Sir Geoffrey Jefferson, F.R.S.: Affections of Trigeminal Nerve.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. P. Wade: Treatment of Cancer of the Skin.

ROYAL EYE HOSPITAL.—5 p.m., Mr. R. P. Crick: Skin Diseases and the Eye.

WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY, St. Mary's Hospital Medical School.—5 p.m., Almroth Wright Lecture by Professor Gerhard Domagk: The Development of the Chemotherapy of Tuberculosis.

Wednesday, June 17

INSTITUTE OF DERMATOLOGY.—4.30 p.m., Dr. H. Haber: Histopathology of Tuberculosis and Syphilis of the Skin.

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Chelsea Hospital for Women, 4.30 p.m., Mr. J. W. A. Hunter: Pregnancy Following Fothergill's Operation.

MIDDLESEX COUNTY MEDICAL SOCIETY.—At Willesden Chest Clinic (Central Middlesex Hospital), 3 p.m., clinical meeting. (Postponed from June 3.)

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. M. G. P. Stoker: Q Fever.

●POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. B. Ackner: Depression.

ROYAL EYE HOSPITAL.—5.30 p.m., Mr. L. H. Savin: Ophthalmic Neurology.

Thursday, June 18

BIRMINGHAM UNIVERSITY.—At Large Anatomy Theatre, Medical School, 4 p.m., Ingleby Lecture by Mr. Stanley Way: Aetiology of Carcinoma of the Body of the Uterus.

EDINBURGH UNIVERSITY: FACULTY OF MEDICINE.—At Surgery Lecture Theatre, University New Buildings, 10 to 11 a.m., Sir Geoffrey Jefferson, F.R.S.: Applied Physiology of Cerebellum.

●HAMPSTEAD GENERAL HOSPITAL.—3 p.m., Dr. Felix W. Brown: Illness in the Family; 4.15 p.m., Mr. H. D. Johnson: Dyspepsia Without an Ulcer.

HONYMAN GILLESPIE LECTURE.—At University New Buildings, Edinburgh, 5 p.m., Dr. Robert Brown: Contracted Pelvis.

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Queen Charlotte's Hospital, 4.30 p.m., Mr. V. O'Sullivan: Acute Inversion of the Uterus.

LONDON JEWISH HOSPITAL MEDICAL SOCIETY.—At 11, Chandos Street, W., 8.30 p.m., (1) A.G.M. (2) Symposium: National Health Service. Mr. C. S. Bangay, Dr. F. Gray, and Dr. M. Sorsby will take part.

NORTH-WESTERN TUBERCULOSIS SOCIETY.—At Hefferston Grange Hospital, 3 p.m., summer meeting.

●POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. J. W. D. Bull: Neuroradiology—Its Scope and Limitations.

ROYAL EYE HOSPITAL.—5.30 p.m., Mr. G. C. Pritchard: Ophthalmic Problems in a Neurological Clinic.

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE.—7.30 p.m., annual general meeting followed by ordinary meeting. Medical films.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Sir Paul Mallinson: postgraduate demonstration in psychiatry.

Friday, June 19

BIRMINGHAM UNIVERSITY.—At Large Anatomy Theatre, Medical School, 4 p.m., Ingleby Lecture by Mr. Stanley Way: Aetiology of Carcinoma of the Body of the Uterus.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. P. F. Borrie: Vascular Diseases.

KENT AND CANTERBURY HOSPITAL.—8 p.m., clinical meeting.

OSLER CLUB OF LONDON.—At 1, Wimpole Street, W., 7.45 p.m., Mr. A. Dickson Wright: Some Royal Case-histories (with slides).

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Professor J. D. Boyd: Pigment Cells in the Body.

●POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. R. I. S. Bayliss: A.C.T.H. and Cortisone.

Saturday, June 20

BIOCHEMICAL SOCIETY.—At Department of Biochemistry, University of Oxford, 11 a.m., scientific papers.

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Hammersmith Hospital, 12 noon, Mr. J. Peel: Diabetes in Pregnancy.

APPOINTMENTS

MANCHESTER REGIONAL HOSPITAL BOARD.—I. M. Gow, M.B., Ch.B., D.A., and R. G. G. Jones, M.B., B.S., D.A., Consultant Anaesthetists to South Manchester Hospital Centre; C. F. Cunniffe, M.B., B.Ch., D.A., Assistant Anaesthetist to Preston and Chorley Hospital Centre; C. St. J. Davies, M.R.C.S., L.R.C.P., D.M.R.D., Assistant Radiologist to Bolton and District Hospital Centre; D. H. Teasdale, M.B., B.S., F.R.C.S., Consultant General Surgeon to Rochdale Hospital Centre; J. F. Donovan, M.R.C.S., L.R.C.P., D.P.M., Consultant Psychiatrist and Deputy Medical Superintendent to Prestwich Hospital, Manchester; R. C. Cunningham, M.B., Ch.B., D.P.H., D.P.M., Consultant Psychiatrist and Medical Superintendent, Royal Albert Hospital, Lancaster; F. M. Benton, M.B., Ch.B., D.M.R.T., Assistant Radiotherapist, Christie Hospital and Holt Radium Institute, Manchester; A. L. Thorburn, M.D., D.P.H., Tuberculosis Physician, Salford and West Manchester Hospital Areas; A. K. Karfoot, M.B., Ch.B., D.A., and R. I. Dixon, M.R.C.S., L.R.C.P., D.A., Consultant Anaesthetists, Barrow and Furness Hospital Centre; J. I. Capper, M.B., Ch.B., Tuberculosis Physician and Medical Officer in Charge of Mass Miniature Radiography Unit based on Preston; H. B. Slater, M.B., Ch.B., Tuberculosis Physician, Oldham and Ashton Hospital Centres.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Benson.—On June 6, 1953, at the Swindon Maternity Hospital, to Joan (formerly Flint), B.D.S., wife of W. G. Benson, M.B., Ch.B., a son.

Carey.—On June 1, 1953, at Burton-on-Trent, Staffs, to Margaret, wife of Dr. A. S. Carey, a sister for Michael—Christine Elizabeth.

Milligan.—On May 28, 1953, at the Ashleigh Private Hospital, Newcastle-upon-Tyne, to Leonore, wife of Councillor Dr. Reid Milligan, a brother for Carole and Judith.

Molloy.—On May 30, 1953, at the University College Hospital, to Audrey Molloy (formerly Mounce), wife of Robert Molloy, M.B., B.S., a daughter—Penelope Anne.

Rickham.—On May 30, 1953, at the Liverpool Maternity Hospital, to Elizabeth (formerly Hartley), wife of P. P. Rickham, M.S., F.R.C.S., a daughter—Susan Diana.

Short.—On May 29, 1953, at the Robroyston Hospital, Glasgow, to Jane, M.D., F.R.F.P.S., wife of Douglas W. Short, F.R.C.S.Ed., of 16, Second Avenue, Millerston, Glasgow, twin sons (one stillborn).

MARRIAGES

Dobson—Dalzell.—On May 30, 1953, at the Parish Church, West Wickham, Kent, Donald Joseph Dobson, M.B., Ch.B., D.C.H., D.Obst.R.C.O.G., of Christchurch, New Zealand, to Ellen Margaret Dalzell, N.Z.R.N., N.Z.R.M.N., of Sefton, New Zealand.

Thomas—Owen.—On June 4, 1953, at Llanbeblig Church, Caernarvon, Robert Garym Thomas, B.M., B.Ch., to Nansi Wyn Owen.

DEATHS

Foulds.—On May 2, 1953, at Cheltenham, Glos, Mathias Frederick Foulds, M.R.C.S., L.R.C.P., Major, R.A.M.C., retired, aged 75.

Greenwood.—On May 2, 1953, at Springfarm House, Redcross, Co. Wicklow, Eire, Henry Walmesley Greenwood, M.R.C.S., L.R.C.P., aged 52.

Gyle.—On May 9, 1953, at Elmbank, Dudhope Street, Dundee, John Burnside Gyle, M.B., Ch.B.

Herdman.—On May 7, 1953, in a nursing-home, Edinburgh, Kenneth Norman Abbott Herdman, M.D., D.A., of 6, Craigmillar Park, Edinburgh.

Hirsch.—On May 5, 1953, at his home, Valentine Robert Hirsch, M.R.C.S., L.R.C.P., aged 61.

Mendez.—On April 27, 1953, at St. Mary's Hospital, London, W., René Leo Mendez, M.B., B.S., of 25a, Cleveland Terrace, London, W.

O'Neill.—On May 6, 1953, Francis O'Neill, L.M.S.S.A., of The Pines, Rhymney, Mon., aged 75.

Reid.—On April 28, 1953, at Arbroath Infirmary, Alexander Reid, M.D., of 40, Addison Place, Arbroath, Angus, formerly of Riverdale, Inverness, aged 80.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Warts and Ringworm from Swimming-baths

Q.—*What are the risks of picking up ringworm of the feet or plantar warts from going to public swimming-baths? Does the chlorine in the water effectively reduce the risk? Are there any simple prophylactic measures which can be advised for children?*

A.—The risk of contracting ringworm infection of the feet or plantar warts in swimming-baths is considerable in spite of chlorination. The best prophylactic is probably the wearing of rubber slippers such as are often worn when bathing at the seaside. Subsequent careful drying of the feet, and powdering, is wise.

Algicides for Swimming-baths

Q.—*What algicide is recommended for a small private swimming-bath to prevent "greening"? The water is chlorinated. What concentration of algicide should be used?*

A.—It is difficult to dogmatize about the prevention of algal growths in swimming-baths, and variations in treatment may be required as experience is gained of a particular pool. The following treatment has proved effective. The quantities given are for a pool containing 100,000 gallons (450,000 litres) of water and should, of course, be varied proportionately to suit the particular case. The chemicals should be evenly distributed through the water. First, 1 lb. (0.45 kg.) of copper sulphate and 2 lb. of ammonium sulphate should be added. This might be done as the bath is being filled to ensure even distribution. After that one of the hypochlorite preparations should be added, so as to give ¼ lb. of available chlorine. The addition of hypochlorite should be repeated at intervals of one or two weeks, according to the condition of the water. The hypochlorite also serves to disinfect the water.

Infectious Lymphocytosis

Q.—*What is known about the aetiology, clinical manifestations and treatment of infectious lymphocytosis?*

A.—Infectious lymphocytosis was first reported by Smith in 1941. He described two types—acute and chronic.

The acute form is a specific infectious disease of unknown aetiology with an incubation period of 12 to 21 days which commonly affects infants and young children. It is characterized by a high leucocytosis due to an increase of normal mature lymphocytes, which persists for about two to seven weeks. The clinical manifestations may be so mild as to escape attention, or there may be symptoms and signs of varying severity such as pyrexia, upper respiratory infection, abdominal pain and tenderness, headache, irritability, and meningismus. Absence of lymphadenopathy and splenomegaly are notable features. The condition runs a benign course with a good prognosis. There is no known specific therapy, and treatment is symptomatic. The use of aureomycin, however, has been claimed to relieve severer cases dramatically.

The chronic form is a non-specific and non-contagious condition. It is frequently met with in paediatric practice and is characterized by a slight to moderate leucocytosis with a lymphocytic preponderance usually persisting for prolonged periods. There is usually a previous history of acute upper respiratory tract infection, followed by a protracted low-grade pyrexia lasting for months. Associated symptoms include anorexia, pallor, listlessness, irritability, fatigability, and para-umbilical pain. Physical signs usually show injected fauces, enlarged and hyperaemic tonsils, post-nasal discharge and slight enlargement of the superficial lymph nodes. This condition does not appear in epidemic form.

Head-wagging and Head-nodding

Q.—*(1) What is the significance of head-wagging in children? A boy aged 5 has indulged in the practice since infancy. He lies on his back and wags his head violently from side to side at the rate of about 100 a minute for perhaps five minutes on end. He does this when dropping off to sleep, and sometimes during the night when apparently asleep. He says he does it because it helps him to go to sleep. The child is otherwise perfectly normal. (2) A baby of 7 months started to have daily head-nodding attacks since being weaned at 4 months. The attacks last about two minutes, and are more usual either just before or just after a meal. If the baby is put down during an attack the eyes roll up. There are no abnormal physical findings. What are the cause and significance of the attacks? What treatment is advised?*

A.—(1) There is no particular significance attaching to the head-wagging habit: it is comparable with head-banging, and will doubtless cease soon. Continuation after the age of 6 years usually indicates some underlying nervous tension. The habit gradually diminishes, then occurs only at times of undue excitement or when the child is below par, and finally ceases. Some children continue till the age of 10 or 11 before losing the habit altogether.

(2) Head-nodding is another habit, but it may occasionally be associated with rickets. If there is any evidence of rickets, vitamin D should be prescribed. The prognosis is good for non-rachitic cases, and no treatment is necessary. The condition seldom persists after the age of 1 year.

Prevention of Serum Anaphylaxis

Q.—*Is the administration of an antihistamine drug half an hour before an injection of serum an acceptable way of preventing anaphylaxis? Alternatively (or in addition), would it help to add 2 minims (0.12 ml.) of 1 : 1,000 adrenaline to the serum before its administration?*

A.—The best method of preventing serum anaphylaxis is to give a small "trial dose" subcutaneously to all patients with a previous history of serum injections or allergic conditions. This is described in detail in the Refresher Course article on "Serum Reactions and Serum Sensitivity Tests."[1] The doctor who takes this precaution, who keeps his cases under observation for at least 30 minutes after injection, and who has a syringe and adrenaline 1 : 1,000 ready for emergency use will generally save lives. By such means the overall incidence of fatal anaphylaxis should be reduced far below the older figure of once in 50,000 to 200,000 administrations of serum quoted by various authorities. The alternative or additional measures suggested are of doubtful efficacy; it would be difficult to demonstrate their value, since the absence of anaphylaxis in extended trials could not be taken as indicating that the new regime was successful. The essential safeguards remain the trial dose, watchfulness for early signs of shock, and adrenaline promptly when required.

REFERENCE

[1] Laurent, L. J. M., and Parish, H. J. (1952). *British Medical Journal*, 1, 1294.

Industrial Fumes and Tuberculosis

Q.—*Is the development or progression of pulmonary tuberculosis a recognized sequel to the inhalation of a large quantity of hydrofluoric acid vapour?*

A.—The influence of irritant fumes and gases on susceptibility to pulmonary tuberculosis is discussed by Rutherford Johnstone.[1] Concerning the effect of hydrofluoric acid, he

states that in a factory where chlorine, sulphur dioxide, hydrofluoric acid, and combinations of phosgene with phosphorus oxychloride and phosphorus trichloride were manufactured "enough [hydrofluoric acid vapour] escaped into the atmosphere so that men with glasses could not work in the rooms, and the window panes were etched to the extent that the wind blew them out of their frames. The films of these men, employed at such work for four to ten or more years, showed no trace of reaction attributable to gas, and the incidence of tuberculosis was no greater than in persons employed in other parts of this large plant. Repeated examinations failed to demonstrate evidence of reactivation of several cases of latent apical disease that occurred in the group." He concluded that there was no evidence that any of the more common industrial fumes or gases alter susceptibility to tuberculosis.

REFERENCE

1 *Occupational Medicine and Industrial Hygiene*, p. 403. St. Louis: C. V. Mosby Company, 1948.

Physiological Clocks

Q.—*What part of the central nervous system is concerned in estimating the passage of time? Normal man is capable of estimating the passage of, say, half an hour with remarkable accuracy, provided that he maintains his concentration. Apart from the disturbances of consciousness (coma, stupor, mescaline intoxication, etc.), are there any known organic neurological disorders in which appreciation of time becomes so distorted that a second passing seems like a millennium?*

A.—Nothing is known of any localized centre in the brain acting as a timekeeper. There is no particular reason why the brain as a whole, or many parts in semi-independence, should not act in this way, if their function tended to vary with time. Apart from sensory appreciation of changes in the external world, the body is provided with a number of possible clocks—for instance, the filling of the bladder or colon, the exhaustion of glycogen stores in the liver, etc. Subjective appreciation of the passage of time is, as is well known, strongly influenced by emotional attitudes. Did not Shakespeare comment on this point? "Who doth he gallop withal? With a thief to the gallows." (*As You Like It*: Act III, Sc. 2.) Appreciation of the passage of time is grossly altered in most disturbances of consciousness, deliria, etc. It is also very dependent on the formation of recent memories, and is therefore affected in Korsakoff's psychosis and similar states. A Korsakoff patient, after an hour's intensive investigation in an interview, may think he has been with the doctor for only a few minutes. There is a condition in which the passage of a second may seem a millennium—mescaline intoxication—but the mechanism is unknown.

Psoralens and Vitiligo

Q.—*What are psoralens, and what is their place in the treatment of vitiligo?*

A.—Reports, particularly in Egyptian and American literature, indicate that certain extracts of the fruit of the plant *Ammi majus*, which grows in Egypt, are effective in the treatment of vitiligo. Attempts are being made to synthesize these substances—ammoidin, ammidin, and majudin. They may be applied to the depigmented areas or may be taken internally, and subsequent exposure to ultra-violet light produces redness and blistering which is followed in a large proportion of cases by normal pigmentation of the affected areas.

Pains in the Feet in Addison's Disease

Q.—*Are severe constant pains in the feet ever a feature in mild Addison's disease? If so, what are their cause and treatment?*

A.—It cannot be said that severe constant pains in the feet are ever a feature of mild Addison's disease. Muscular cramps, usually in the calves, occur as a result of loss of sodium chloride and clear up with treatment with deoxycortone acetate and salt. It is possible that pains in the feet may similarly arise, although it is unlikely in *mild* Addison's disease. Another suggestion is that the pains in question may be due to flat feet, produced by the muscular weakness which is a characteristic feature of Addison's disease.

Sleep-walking and Epilepsy

Q.—*Is there any relationship between sleep-walking and the later development of epilepsy? What treatment is advised for sleep-walking of very recent origin in a boy of 6?*

A.—It is obviously possible that in an individual case sleep-walking might occur as a post-epileptic automatism after a nocturnal fit. Such an occurrence would be most unusual, and it must be remembered that sleep-walking is very common. So far as is known, there is no general relationship between sleep-walking and epilepsy.

Often the best treatment of sleep-walking is no treatment at all. This is so when it occurs only on isolated occasions in an otherwise well-adjusted child. The doctor's job is then to reassure the over-anxious parents. He can tell them that about 50% of children walk in their sleep once or twice in their lives, that it is in fact normal, and very rarely indeed likely to involve a risk. If reasonable safeguards are taken against such dangers as falling downstairs, there need be no concern. If sleep-walking is frequent and persistent, rather more notice should be taken. It may then be but one sign of a more general nervousness—caused by an element of emotional discord in the home, for instance—which will need investigation and treatment. The symptom itself often responds to hypnosis and post-hypnotic suggestion.

NOTES AND COMMENTS

Heavily Furred Tongue.—Dr. A. LOWNDES YATES (Canford Cliffs) writes: The clinical picture described in this question ("Any Questions?" May 9, p. 1061) would apparently correspond to that found in invasion of the epithelium of the tongue with the penetrating form of monilia and/or with the fungus torula, since both not infrequently exist together. The forms of monilia and torula which are present in normal healthy mouths produce no symptoms, but in the penetrating forms the spores invade first the superficial and later the deeper layers of epithelium, and in the latter case cause ulceration. Such an invasion of the epithelium by the spores is often accompanied by the symptoms of oesophagitis, with which certain of the symptoms mentioned in the clinical history of the case would correspond. A smear taken from the tongue and stained would, if the diagnosis of monilial or torulal infiltration is correct, show some of the cells derived from deeper layers of epithelium which have been invaded by the spores. If this provisional diagnosis is confirmed by microscopical examination of a smear, the most satisfactory though messy treatment is by means of application of coloured dyes to the surface of the tongue, while about three grains of sulphathiazole applied as powder to the contact surface of the dentures may hasten the disappearance of the symptoms, which, however, do not yield with great rapidity to any form of treatment with the exception of radiation, which latter is apt to be followed by distressing dryness of the mouth which lasts for weeks or months.

Correction.—In our leading article "Homage to Lind" (June 6, p. 1265) we should have added that the Royal Navy was also represented by Surgeon Vice-Admiral Sir Alexander Ingleby-Mackenzie, medical director-general, who took the chair at the afternoon session on May 22 and read an address on Lind.

All communications with regard to editorial business should be addressed to THE EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1. TELEPHONE: EUSTON 4499. TELEGRAMS: *Aitiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.

Authors desiring REPRINTS should communicate with the Publishing Manager, B.M.A. House, Tavistock Square, W.C.1, on receipt of proofs. Authors overseas should indicate on MSS. if reprints are required, as proofs are not sent abroad.

ADVERTISEMENTS should be addressed to the Advertisement Manager, B.M.A. House, Tavistock Square, London, W.C.1 (hours 9 a.m. to 5 p.m.). TELEPHONE: EUSTON 4499. TELEGRAMS: *Britmedads Westcent, London.*

MEMBERS' SUBSCRIPTIONS should be sent to the SECRETARY of the Association. TELEPHONE: EUSTON 4499. TELEGRAMS: *Medisecra, Westcent, London.*

B.M.A. SCOTTISH OFFICE: 7, Drumsheugh Gardens, Edinburgh.